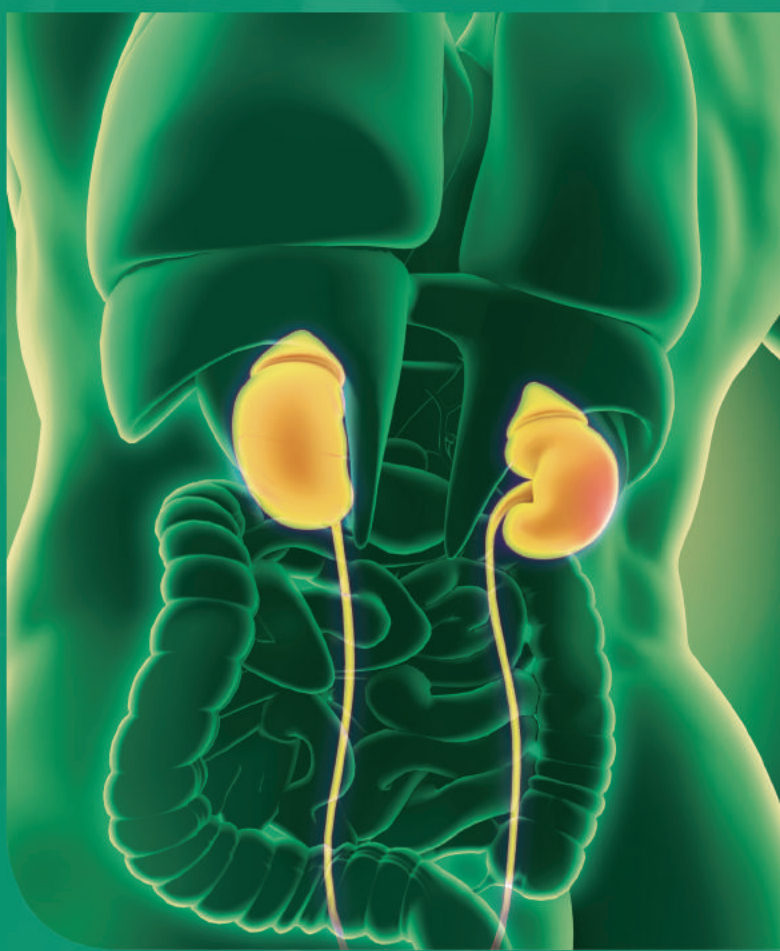
Oxford Textbook of Clinical Nephrology

FOURTH EDITION

Edited by
Neil Turner
Norbert Lameire
David J. Goldsmith
Christopher G. Winearls
Jonathan Himmelfarb
Giuseppe Remuzzi



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Oxford Textbook of

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VOLUME 1

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Preface

We have almost completely rewritten the *Oxford Textbook of Clinical Nephrology* for its fourth edition. That was a big decision for a very successful book, but there were several important drivers.

Huge developments in nephrology and medicine more broadly were only part of the reasoning. First, we wanted a text that would adapt easily to presentation in multiple formats—on paper and also electronically on different devices. Shorter (but more) chapters seemed an important part of this, but meant reviewing the organization of the entire book. However, this also helped us to meet our second objective, which was to make it easier to get quick answers to specific questions. And third, we wanted a structure that would aid updating in the future, both on paper and electronically.

Our authorship and editorship are substantially changed and even more international than before, with representation from every continent except Antarctica. Our coverage of global topics is substantially enhanced. There is an entirely new section on genetic diseases, and substantially increased coverage for the patient with a renal transplant. We have completely revised and combined previous sections on tubular disorders and electrolytes, achieving greater clarity and reduced duplication. There is new material on renal disease in childhood and old age, together with a completely new set of chapters on renal disease in pregnancy.

The book is no longer but we believe it is substantially enhanced. This has been a huge project for the editors, project managers, and production team—but ultimately, a very rewarding one. We hope you will agree that it has been worthwhile.

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SECTION 1

Assessment of the patient with renal disease

CHAPTER 1

Epidemiology of kidney disease

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Basic epidemiology principles in nephrology

Introduction

Epidemiology is the study of the distribution, determinants, and frequency of disease in populations or settings (Rothman, 1981, 2002). Therefore, epidemiological studies assess the extent of disease, risk/causal factors, natural history, prognosis, prevention/treatment strategies, and the potential for new policies to prevent disease or improve outcomes (Rothman, 2002).

Epidemiological research helps to inform evidence-based medicine by identifying risk factors for disease and to determine optimal treatment approaches; it is the cornerstone of public health research and of preventive medicine. The identification of unbiased causal relationships between exposures (risk factors or interventions) such as hypertension or the use of antihypertensive medication and outcomes like morbidity and mortality is therefore an important aspect of epidemiology. This section will discuss some epidemiological concepts, methods, and their application to clinical research in nephrology.

Research questions

Defining an appropriate research question requires familiarity with knowledge gaps in the subject area to judge if a question is feasible, interesting, novel, ethical, and relevant (FINER criteria) (Hulley et al., 2007). Whereas the FINER criteria highlight general aspects of research questions, the development of a specific research question may follow the PICO format, in which P stands for the population (or problem) of interest, I for the intervention (or any other exposure), C for the comparison group, and O for the outcome of interest. Some suggest a PICOT approach, adding a T for the follow-up time to assess outcome (Haynes et al., 2006). An example of a question framed according to PICOT is 'In dialysis patients (*P*), what is the effect of statins (*I*) compared to placebo (*C*) on cardiovascular mortality (*O*) after 4 years of follow-up (*T*)?' A research question has implications for the choice of the study design—which will in turn determine the analytical methods.

Study designs

Fig. 1.1 shows an algorithm for the classification of study designs in clinical research (Grimes and Schulz, 2002). Study design is an important aspect of study quality. Studies can be classified into experimental and observational ones depending on whether or not exposures like therapy were assigned by the investigators. Random allocation of exposures is important to prevent selection bias by the clinician (also known as 'confounding by indication') (Stel et al., 2007) occurring, when clinicians provide a specific therapy because of preconceived ideas about which therapy is best. Therefore, when it comes to studies on the effects of therapy or other interventions, randomized controlled trials (RCTs) are the gold standard. This was exemplified by RCTs showing a lack of effect or even harmful effects of using high target haemoglobin level in chronic kidney disease (CKD) patients as opposed to using a lower target (Drueke et al., 2006; Singh et al., 2006), whereas the majority of observational studies had suggested that higher haemoglobin levels were associated with favourable outcomes.

On the other hand, observational studies may answer questions on aetiology, diagnosis, prognosis, and adverse effects. In addition, they may provide answers on the effects of therapy where RCTs are not possible, inappropriate, inadequate, or unnecessary (Black, 1996). The effect of transplantation as compared to dialysis cannot be determined through an RCT, as allocation of renal grafts depends on other factors like HLA-matching. Where there is no comparison (control) group (as in case reports or case series), observational studies are called descriptive and where there is a comparison group they are referred to as analytical. Finally, the temporal direction of analytical observational studies determines the type of study. Cohort studies like the Dialysis Outcomes and Practice Patterns Study (DOPPS) determine the exposure of subjects to risk factors at the start of inclusion and then look forward in time to observe the occurrence of outcomes. They may provide a wealth of data which enable the investigator to study not only multiple outcomes but—unlike RCTs—also multiple exposures. In contrast, case–control studies compare cases (those with the disease or other outcome of interest) with controls (those without the outcome of interest) and then look back in time for exposures that might have caused the outcome. In nephrology, case–control studies are uncommon. Nevertheless, this study type is very efficient for studying potential risk factors for rare outcomes that may take a long time to develop, for example, CKD. By going back in time and looking for particular exposures like analgesics one may find associations between outcomes and these exposures. In such a case, prospective cohort studies are less efficient as one will need a very high number of subjects and a very long time to acquire an equal number of cases. Finally, cross-sectional studies examine the presence of an exposure and that of the outcome at the same moment in time. In most cases this simultaneity makes it difficult to determine which is the cause and which is the consequence, in other words, this design may induce a chicken-and-egg problem. Table 1.1 describes the strengths and weaknesses of different study designs (Jager et al., 2007).

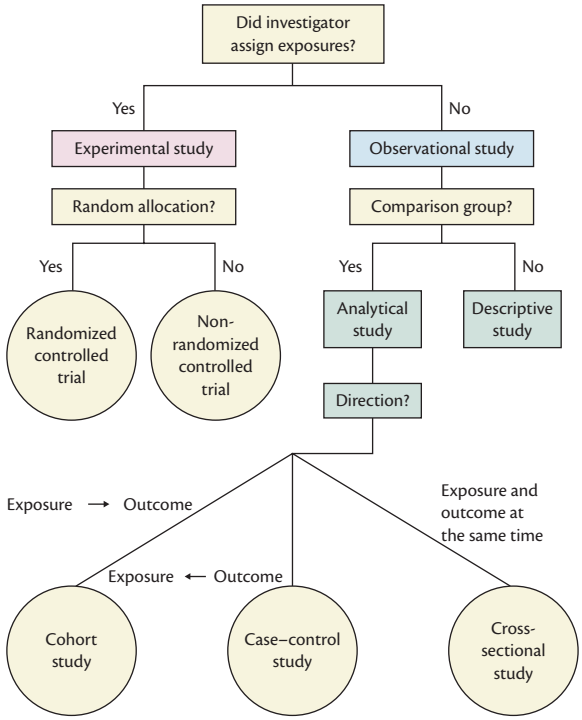

Fig. 1.1 Algorithm for the classification of study designs in clinical research. Reprinted from *The Lancet*, 359(9300), Grimes DA, Schulz KF, An overview of clinical research: the lay of the land, 57–61, 2002, with permission from Elsevier.

Table 1.1 Strengths and weaknesses of frequently used study designs

Study design	Strengths	Weaknesses
Case report/ case series	◆ First form of publication for new diseases, rare adverse events, or manifestations of disease ◆ Fast and inexpensive ◆ Hypothesis generating	◆ Very limited potential to make causal inferences, unless in dramatic cases ◆ Selection bias
Cross-sectional study	◆ Can assess prevalence and burden of disease ◆ Fast and inexpensive ◆ Hypothesis generating	◆ Very limited potential to make causal inferences, because the time order of exposure and outcome cannot be determined ◆ Selection bias ◆ Survival bias
Case–control study	◆ Efficient study design ◆ Very suitable for studying rare outcomes and outcomes that take a long time to develop ◆ Can study multiple exposures ◆ Relatively inexpensive ◆ Hypothesis generating	◆ Some potential to make causal inferences ◆ Can study only one outcome at the time ◆ Choice of controls needs careful attention ◆ Selection bias ◆ Recall bias
Cohort study	◆ Can study multiple exposures, uncommon exposures and multiple outcomes ◆ Hypothesis generating	◆ Some potential to make causal inferences ◆ If done prospectively, more expensive ◆ If done prospectively, may take a long time to complete ◆ Selection bias
Randomized controlled trial	◆ Important potential to make causal inferences	◆ Can study multiple outcomes, but only one exposure ◆ Very expensive ◆ Limited generalizability when making use of restrictive in- and exclusion criteria ◆ Selection bias

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Knowledge derived from different studies published on a specific topic can be summarized in a systematic review (Noordzij et al., 2009). In contrast to narrative reviews, systematic reviews use explicit and reproducible methods for searching the literature and a critical appraisal of individual studies. This systematic methodology minimizes bias. Sometimes systematic reviews include a meta-analysis. This is a mathematical synthesis of the results of those individual studies in which more weight is given to results of studies with more events and sometimes to studies of higher quality.

Criteria for the reporting of studies using particular designs have been summarized in statements like CONSORT (Schulz et al., 2010) for RCTs, STROBE (von Elm et al., 2007) for observational studies, and PRISMA (Moher et al., 2009) and MOOSE (Stroup et al., 2000) for their respective meta-analyses. Such statements assist authors in writing such reports, help editors and peer reviewers in reviewing manuscripts for publication, and aid readers in critically appraising the quality of published studies.

Measures of disease occurrence

Different measures may be used to describe how often a disease (or other health outcomes) occurs in a population (Jager et al., 2007). Incidence expresses the development of new cases and is mostly used against the background of prevention, to assess disease aetiology or to determine risk factors. Depending on the study question, incidence may be reported as risk or as incidence rate. The latter is preferred when studying a dynamic population or when the observation period is sufficiently long for competing risks (like death from causes other than the outcome under investigation) or loss to follow-up to play a significant role. Determining the incidence rate of a treatment like renal replacement therapy (RRT) is straightforward. When determining the incidence of a chronic condition like CKD, problems may arise, as it is unfeasible to identify newly developed CKD in all individuals who were initially free from this disease.

Prevalence on the other hand is the number of existing cases. It reflects the burden of the disease in a population and can be used for the planning of healthcare facilities. Again, the assessment of the prevalence of a treatment like RRT is relatively uncomplicated. However, the assessment of the prevalence of stages 3–5 of CKD according to the National Kidney Foundation Kidney Disease

Outcomes Quality Initiative (NKF-KDOQI) 2002 and Kidney Disease: Improving Global Outcomes (KDIGO) 2004 definition only needs an estimated glomerular filtration rate (eGFR), whereas that of stages 1–2 CKD also requires albuminuria testing.

Finally, measures of disease occurrence are used to study causes of disease or effects of risk factors. One way to estimate the size of such an effect is the calculation of the ratio between the disease occurrence (e.g. cardiovascular disease) in those being exposed to the risk factor (e.g. diabetes mellitus) and those not exposed to the risk factor. The resulting 'relative risk' is an example of this measure of effect.

Bias and confounding

Bias is a systematic error in the design or conduct of a study (Tripepi et al., 2008). It may affect study validity in several ways, for example, through methods used by the investigator in recruiting study subjects or through factors affecting study participation (selection bias) or through systematic distortions in the collection of exposures or outcomes (information bias).

Selection bias may, for example, occur when investigators performing an RCT use very strict inclusion criteria so that only relatively healthy subjects will be included in the study. The study results in this 'selected' group may not necessarily be generalized to very sick patients. Information bias on the other hand may, for instance, be induced when inaccurate instruments systematically over- or underestimate exposures like blood pressure or when in case–control study diseased individuals (cases) much better remember potentially harmful exposures than non-diseased individuals (controls). The latter is called recall bias.

Confounding is a 'blurring' of effects, obscuring the 'real' effect of an exposure on outcome (Jager et al., 2008). For example, the inverse association between total cholesterol level and mortality in dialysis patients was likely the result of confounding by systemic inflammation and malnutrition (Liu et al., 2004). For this reason, in aetiological studies, investigators do their best to prevent confounding, for example, by randomization, or to control confounding. A frequently used method to control for confounding is including the confounding variable into multivariate analysis. However, before a variable qualifies as a confounder it should fulfil three criteria: (1) be a risk factor for the outcome studied, (2) be associated with the exposure, and (3) not be an effect of the exposure (be in the causal pathway). The last criterion is important to avoid 'over-adjustment' through which an investigator may take away part of the real effect of an exposure and may introduce bias instead of preventing it. For example, in a study on the association between body mass index (BMI) and the risk of ESRD (Hsu et al., 2006) the authors were right in not adjusting for blood pressure, as blood pressure can be considered in the causal pathway between BMI and end-stage renal disease (ESRD). Therefore, before including them in a multivariate analysis, the criteria for confounding should be checked carefully for every variable in every association studied.

Regression analysis

This statistical technique describes the dependence of the outcome ('dependent') variable from the value of one or more exposure variables ('independent' variables). Regression can be used for univariate analysis (without controlling for confounding) and multivariate analysis (with adjustment for confounding). Table 1.2 shows that the choice for the type of regression analysis depends on the type of outcome studied, but not on the type of exposure variables that may be included in the analysis. Linear regression analysis demands that the outcome variable is continuous, for example, the 3-year risk of cardiovascular events. Logistic regression, on the other hand, is needed to study categorical outcomes such as whether or not patients are compliant with therapy prescription. Finally, survival analysis is used to study 'time-to-event' data like time to death, to first renal transplant, or to myocardial infarction.

Table 1.2 Types of regression analysis

	Outcome variable (dependent variable)	Exposure variable (independent variable)	Measure of effect
Linear	Continuous	Continuous or categorical	Relative risk
Logistic	Categorical	Continuous or categorical	Odds ratio
Survival analysis	Time-to-event	Continuous or categorical	Hazard ratio

In survival analysis, the survival times of subjects not experiencing the event of interest are being censored. The Kaplan–Meier method, being the most popular method for survival analysis, provides estimates of survival probabilities and may compare survival between groups. The method can, however, only study the effect of one exposure at the time and it cannot provide an effect size. Multivariate survival analysis and effect estimation therefore need other techniques like Cox proportional hazards regression. The measure of effect of Cox regression is the hazard ratio. Both the odds ratio and the hazard ratio can be interpreted as relative risks.

Screening

Investigating apparently healthy individuals to detect unrecognized early stages of disease allows measures to be taken to prevent or slow down progression and reduce (premature) death in those affected (Grootendorst et al., 2009). In 1968, the World Health Organization (WHO) published ten criteria to facilitate the selection of conditions that are suitable for screening (Wilson and Jungner, 1968) which have been supplemented with additional criteria thereafter (Andermann et al., 2008). These criteria should be taken into account when considering screening for conditions like CKD.

Evaluation of screening programmes may suffer from bias. For example, those who volunteer to be tested for CKD may have a family history of kidney disease resulting in a high detection rate. In addition to this form of selection bias, those who are diagnosed by screening more frequently include those with slowly progressive disease, as those with poor prognosis are less likely to be picked up by screening because of their higher mortality risk. This length bias will provide a 'better' prognosis to those identified in a screening programme, even if screening has no effect on prognosis. Similarly, earlier diagnosis through screening may lead to an apparent increase in survival time. This phenomenon is known as lead-time bias (Grootendorst et al., 2009).

Epidemiology of acute kidney injury

(See also Chapter 220.)

Definition, classification, and evaluation of acute kidney injury

Acute kidney injury (AKI) is a clinical syndrome characterized by a sudden onset of reduced kidney function, and is manifested by increased serum creatinine (SCr) or a reduction in urine output (Hou and Cohen, 1985; Bellomo et al., 2004; Lameire et al., 2005; Cerda, 2008). Until recently, there was no standard definition for AKI, leading to highly variable estimates of the incidence, prevalence, and prognosis of this syndrome (Lameire et al., 2005). Prior to 2004, the key definition in use was based on the WHO International Classification of Disease (ICD) codes, which are used mainly for administrative purposes in the healthcare systems of developed countries. Criteria based on various SCr values and/or the receipt of dialysis were also commonly used (especially by clinicians in hospital settings (Mehta and Chertow, 2003; Lameire et al., 2006))—although such definitions vary widely across settings, populations and institutions (Mehta and Chertow, 2003; Mehta et al., 2007).

The absence of a standardized definition of AKI led to the development of consensus criteria by the Acute Dialysis Quality Initiative (ADQI), which are known as the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) 2004 criteria (Van Biesen et al., 2006; Mehta et al., 2007). The RIFLE scheme is based on two important parameters: changes in SCr or eGFR from baseline and urine output at specific points in time (Table 1.3) (Mehta et al., 2007). This classification was subsequently modified and the term 'acute renal failure' was replaced with 'acute kidney injury' to cover the entire spectrum of acute renal dysfunction from mild changes in renal function to the use of dialysis (Table 1.3) (Van Biesen et al., 2006). This standardization of terminology facilitates comparison between settings. However, the central role of quantitative changes in urine output in the scheme may make it most applicable to critical care units or other closely monitored settings. Although the RIFLE criteria were validated in over half a million AKI patients globally (Cerda et al., 2008b; Cruz et al., 2009), the system was subsequently revised by another international group (the Acute Kidney Injury Network (AKIN)). The AKIN scheme uses slightly broader criteria than the RIFLE system, and reflects the clinical significance of relatively small rises in SCr (Table 1.3) (Mehta et al., 2007; Cruz et al., 2009). Of note, it appears that RIFLE may be slightly better than AKIN for risk prediction and prognostication (Ricci et al., 2008).

To reconcile these minor differences, the International Society of Nephrology (ISN) and KDIGO (Anonymous, 2012), has brought together international experts from multiple specialties to harmonize the RIFLE and AKIN criteria and produce a truly global definition and staging system (Anonymous, 2012)—further enabling future comparisons of the incidence, outcomes, and efficacy of therapeutic interventions for AKI (Table 1.3).

Limitations and pitfalls for AKI definition

It is important to recognize that no single definition of a clinical syndrome is ideal; the purpose of establishing a consensus definition is to establish the presence/absence of disease, provide an index of severity, and relate these to prognosis and outcome

Table 1.3 Definitions/classification for AKI

Classifications	Criteria	Urine output criteria
KDIGO		
Stage 1	Increase ≥ 26 μmol/L within 48 h or increase ≥ 1.5 to 1.9 × reference SCr	< 0.5 mL/kg/h for > 6 consecutive h
Stage 2	Increase ≥ 2 to 2.9 × reference SCr	< 0.5 mL/kg/h for > 12 h
Stage 3	Increase ≥ 3 × reference SCr or increase 354 μmol/L or commenced on RRT irrespective of stage	< 0.3 mL/kg/h for > 24 h or anuria for 12 h
RIFLE		
Risk	Increased creatinine × 1.5 or GFR decrease > 25%	< 0 .5 mL/kg/h × 6 h
Injury	Increased creatinine × 2 or GFR decrease > 50%	< 0 .5 mL/kg/h × 12 h
Failure	Increase creatinine × 3 or GFR decrease > 75% or creatinine 4 mg/dL (acute rise of 0.5 mg/dL)	< 0.3 mL/kg/h × 24 h (oliguria) or anuria × 12 h
Loss	Persistent ARF = complete loss of renal function > 4 weeks	
ESRD	End-stage renal disease	
AKIN		
Stage 1	Increase ≥ 26 μmol/L within 48 h or increase ≥ 1.5–1.9 × reference SCr	< 0.5 mL/kg/h for ≥ 6 h
Stage 2	Increase ≥ 2–2.9 × reference SCr	< 0.5 mL/kg/h for ≥ 12 h
Stage 3	Increase ≥3 × reference SCr or increase≥ 354 μmol/L with an acute rise of at least 44 μmol/L or initiation of RRT	< 0.3 mL/kg/h for ≥ 24 h or anuria ≥ 12 h
ICD 9 codes		
ARF	ARF without dialysis Any of the following: 584.5: ARF, with lesion of tubular necrosis 584.6: ARF, with lesion of renal cortical necrosis 584.7: ARF, with lesion of renal medullary (papillary) necrosis 584.8: ARF, with other specified pathologic lesion in kidney	
ARF-D	ARF with dialysis: ARF code as above *plus* any of the following codes: 584.9: ARF, unspecified V39.95: haemodialysis V45.1: renal dialysis status (patient requires intermittent renal dialysis; presence of arteriovenous shunt) V56.0: extracorporeal dialysis (dialysis (renal) not otherwise specified) V56.1: fitting and adjustment of extracorporeal dialysis catheter	

ARF = acute renal failure; ARF-D = acute renal failure with dialysis; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; RRT = renal replacement therapy; SCr = serum creatinine.

(Rothman, 2002). In addition to lack of standardization, definitions used before RIFLE/AKIN did not facilitate detection of milder forms of AKI—which are highly prevalent and also associated with adverse clinical outcomes (Yong et al., 2011). Despite the advantages of the RIFLE/AKIN criteria, these definitions also have some limitations (Van Biesen et al., 2006; Cerda et al., 2008b; Yong et al., 2011). First, the use of 6-hour and 12-hour urine output criteria make RIFLE difficult to use for retrospective studies of AKI, since such data are not routinely collected (Van Biesen et al., 2006; Srisawat et al., 2010). Second, there is not necessarily any correlation between the SCr and urine output criteria for severity of AKI, as patients often present with high SCr but good urine output or vice versa. Third, SCr/eGFR criteria are based on change from a baseline value (which is not always available). Fourth, eGFR is valid only in steady-state conditions—which is certainly not the case in AKI (Srisawat et al., 2010). Fifth, recent studies have shown that smaller changes in SCr than those specified by the RIFLE criteria (such as an absolute increase of 0.3 mg/dL) are also associated with poor outcomes (Srisawat et al., 2010). These limitations have been partially addressed by AKIN (Van Biesen et al., 2006; Srisawat et al., 2010)—which has eliminated the eGFR criterion and explicitly recognized the adverse prognostic values associated with very small changes in SCr (Van Biesen et al., 2006).

Risk factors and causes for AKI

A partial list of predisposing factors (risk factors) and causes for AKI is shown in Fig. 1.2; the incidence and likelihood of which vary according to the clinical setting (hospital vs community; developed vs developing countries) (Joannidis and Metnitz, 2005; Lameire et al., 2005, 2006). For instance, acute tubular necrosis (ATN) due to sepsis is the most common cause of AKI in the critical care setting, accounting for up to 35–50% of all cases of AKI (Lameire et al., 2005). In a large-scale study, the Madrid Acute Renal Failure Study in Spain, ATN was the cause of AKI in 75.9% of intensive care unit (ICU) patients compared to 37.6% in non-ICU patients (Liano and Pascual, 1996). ATN in hospitalized patients is more likely to be multifactorial, with hypotension and nephrotoxins as important causes in addition to sepsis and surgery (Cerda et al., 2008b). For community-acquired AKI, prerenal or acute-on-chronic renal failure is common and usually occurs as the result of dehydration or drug-induced causes as seen with the use of non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs) (Cerda, 2008; Cerda et al., 2008b). Elderly people and patients with multiple comorbidities such as diabetes are at particularly high risk of developing community-acquired AKI (Cerda, 2008) (Fig. 1.2). AKI is being conceptualized as a spectrum as obtained in CKD from normal to increased risk, decreased function to kidney failure, and/or death (Fig. 1.3).

Descriptive epidemiology of AKI

(See also Chapter 220.)

There is a paucity of high-quality population-based data on the incidence of AKI—whether community- or hospital-acquired (Cerda et al., 2008b; Yong et al., 2011). Before the advent of the RIFLE/AKIN classification systems, the reported incidence of AKI varied from 1% to 30% across studies (Lameire et al., 2005; Waikar et al., 2008). As reviewed by Waikar et al. (2008), the incidence of AKI also shows considerable variation based on the clinical setting (Lameire et al., 2005, 2006). The prevalence of hospital-acquired AKI is reported to be about five to ten times greater than community-acquired AKI, with reported rates of AKI of 5–7% of hospitalized patients (Hsu et al., 2007; Waikar et al., 2008; Yong et al., 2011). In country-specific data, the reported prevalence of AKI in the United States ranges from 1% (community acquired) to 7.1% (hospital acquired) of all hospital admissions (Lameire et al., 2005, 2006). The population incidence of AKI from UK data ranges from 172 pmp to 486–630 pmp (Yong et al., 2011). Early studies from the 1990s reported that the annual incidence rates of community-acquired AKI varied from 22 to 620 pmp, with most studies using the receipt of dialysis or SCr ≥ 300 or 500μmol/L to define AKI (Lameire et al., 2005; Yong et al., 2011). The reported incidence of AKI varies considerably and depends on how AKI was defined, the setting where it occurred, population studied, and also whether patients with *de novo* CKD developing AKI were included. For instance, the reported incidence varies from 140 to 620 pmp across countries (Feest et al., 1993; Liano and Pascual, 1996; Stevens et al., 2001; Waikar et al., 2006). In the United Kingdom, the reported incidence was 620 pmp/year among patients with SCr ≥ 300 μmol/L (Stevens et al., 2001) and 140 pmp/year in those with SCr > 500 μmol/L (Feest et al., 1993). In Spain, the incidence of AKI was 209 pmp from data of patients in tertiary care hospitals and SCr > 177 μmol/L (Liano and Pascual, 1996). In the United States, the reported incidence was 288 pmp, but ICD-9 codes rather than SCr criteria were used to define AKI (Waikar et al., 2006).

The incidence of community-acquired AKI appears to be increasing: the incidence of non-dialysis-dependent AKI and dialysis-dependent AKI increased from 322.7 to 522.4 and 19.5 to 29.5 per 100,000 person-years, respectively, between 1996 and 2003 (Hsu et al., 2007). The rising incidence of community-based AKI over time likely reflects the ageing general population, the increasing prevalence of chronic comorbidity (including CKD), and increasing utilization of nephrotoxic agents (such as intravenous radiocontrast, aminoglycosides, NSAIDs, ACEIs/ARBs, and chemotherapeutic agents) among outpatients (Cerda, 2008; Yong et al., 2011). In ICU settings, an estimated 5–20% of patients experience an episode of AKI during the course of their illness, and AKI accounts for nearly 10% of all ICU bed-days (Joannidis and Metnitz, 2005; Yong et al., 2011). However, AKI usually coexists with other acute illnesses, since the incidence of AKI as single-organ failure in ICU patients is as low as 11% compared to 69% in non-ICU settings. There have been several studies on epidemiology of AKI in various settings (Waikar et al., 2008).

AKI in special populations

(See also Chapters 239–241.)

There are major differences in the epidemiology of AKI between geographic regions (especially in developing vs developed nations), and also across sociodemographic categories defined by age (elderly, children), gender, and social deprivation (Lameire et al., 2005, 2006, 2013; Zappitelli et al., 2008). Numerous reviews outline differences and similarities in the causes and consequence of AKI between developed and developing regions, analyse the practical implications of the identified differences, and make recommendations for management (Lameire et al., 2005, 2006, 2013). In developing countries, the reported incidence of hospital-based AKI is much lower than in developed countries (Lameire et al., 2006), likely because AKI is under-recognized in developing countries (Lameire et al.,

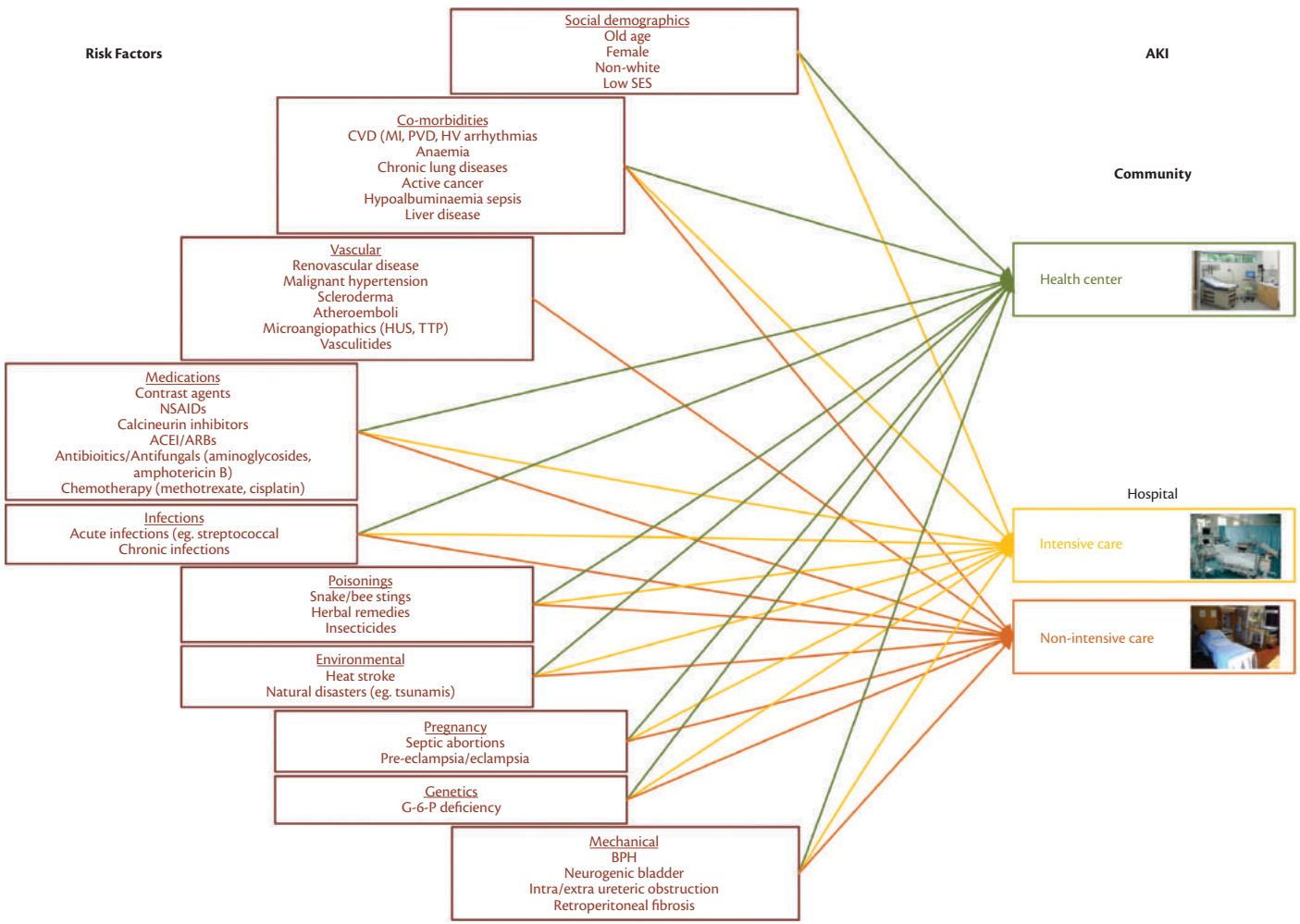

Fig. 1.2 Risk factors for AKI.

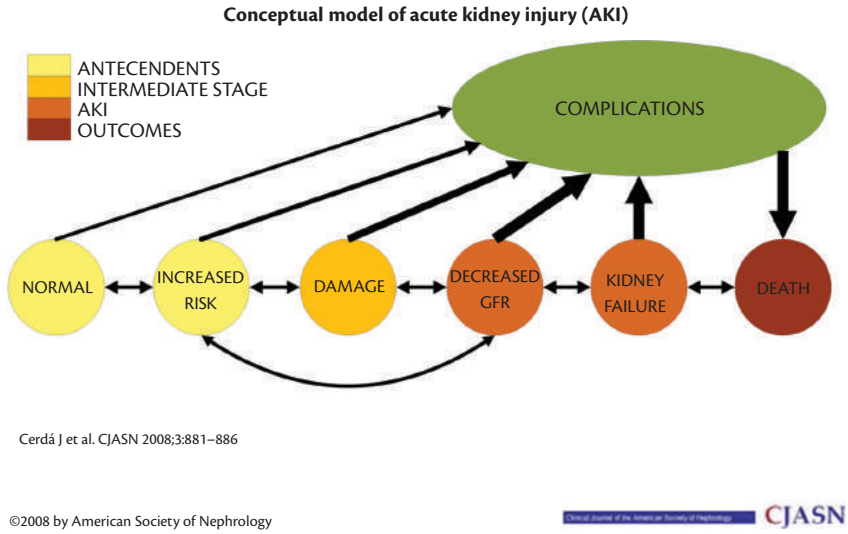

Fig. 1.3 Conceptual model for AKI.
Drawn from Cerda, J., Lameire, N., Eggers, P. *et al.* Epidemiology of acute kidney injury. *Clin J Am Soc Nephrol*, 2008; 3:881–886.

2006; Cerda et al., 2008a) due to reduced access to care, delayed referral to specialist services, and lack of dialysis services (Cerda et al., 2008a). Patients with AKI in developing nations tend to be substantially younger, are more likely to have infection-related glomerulonephritis, and are more likely to be female compared with those in the developed world (Lameire et al., 2006; Cerda, 2008)—the latter may be partially due to a high incidence of obstetrics complications such as septic abortion (Cerda et al., 2008a). In addition, seasonal increases in the risk of AKI may be observed in developing nations—due to corresponding variation in the risk of malaria, heat stroke, animal envenomation, and diarrhoeal diseases (Lameire et al., 2006; Cerda et al., 2008a; Lameire et al., 2013). Thus, the prerenal and toxic factors predominate as AKI risk factors in developing countries (Lameire et al., 2006). Preventive opportunities are often missed because of failure to recognize the risk factors and late presentation for treatment (Lameire et al., 2006). For instance, a firm aetiology for AKI cannot be established in many instances because of a lack of appropriate laboratory and technical support (Lameire et al., 2006, 2013). Regardless of the setting, most cases of AKI in children are secondary to prerenal causes from acute dehydration, major surgeries, and sepsis (Lameire et al., 2005). In contrast, the elderly are more susceptible to AKI due to multiple comorbidities and lower renal functional reserve associated with ageing (Lameire et al., 2006; Yong et al., 2011).

Prognosis and outcomes

(See Chapter 237.)

AKI in hospitalized patients is associated with poor prognosis, and mortality ranges from 10% to 80% depending on the population studied (Waikar et al., 2008). Patients who present with uncomplicated AKI have a mortality of < 10% (Waikar et al., 2007). In contrast, patients presenting with AKI and other organ failure have been reported to have short-term mortality of > 50% (Ricci et al., 2008; Waikar et al., 2008; Alkandari et al., 2011; Yong et al., 2011; Singbartl and Kellum, 2012), especially if acute dialysis is required, which may be associated with short-term mortality of up to 80% (Lameire et al., 2005; Yong et al., 2011). As in CKD, lower eGFR and heavier proteinuria independently increase the risk of AKI. However, the excess risk of mortality associated with an episode of AKI is actually lower among people with lower baseline eGFR and heavier proteinuria, as compared to those with normal kidney function (James et al., 2010).

Epidemiology of chronic kidney disease

Definition, classification, and evaluation of CKD

(See Chapter 94.)

As for AKI, several terminologies such as 'chronic renal failure', 'chronic renal insufficiency', 'chronic kidney failure', 'progressive renal failure or insufficiency', and 'pre-dialysis' were used in the past to denote CKD, with further subclassification mainly by the underlying aetiology (Anonymous, 2002, 2007; Levey et al., 2011; Levey and Coresh, 2012).

In 2002, the NKF-KDOQI released guidelines for the diagnosis and classification of CKD (Anonymous, 2002). These criteria standardized the nomenclature of CKD and the laboratory evaluation of kidney disease, documented the associations between level of kidney function and multiple complications, and facilitated risk stratification for adverse outcomes of CKD (Anonymous, 2002). The KDOQI criteria defined CKD by structural or functional abnormalities of the kidney for at least 3 months, manifested by either kidney damage (often persistent albuminuria) with or without a decreased eGFR to a value < 60 mL/min/1.73m^2, or a decreased eGFR with or without other evidence of kidney damage for at least 3 months (Anonymous, 2002) (Box 1.1). This staging was later modified and endorsed by the international KDIGO in 2004 according to severity and treatment (Levey et al., 2011). This was further updated in 2012 following a decade of further research and practice since the publication of the initial guidelines (Stevens et al., 2013) (Table 1.4). The new classification system now incorporates a three-dimension operational definition for CKD that includes cause, GFR category, and albuminuria category (CGA). The underlying cause of CKD was added to the definition in order to highlight the importance of this information for management and prognostication (Table 1.5). Offsetting these

Box 1.1 Stages of CKD by NKF-KDOQI definition

- Stage 1: patients with normal glomerular filtration rate (GFR), but some evidence of kidney damage as manifested by albuminuria/proteinuria, haematuria, or histological changes
- Stage 2: mild CKD characterized by GFR of 89–60 mL/min/1.73 m^2 with some evidence of kidney disease as manifested by albuminuria/proteinuria, haematuria, or histological changes
- Stage 3: moderate CKD with GFR 59–30 mL/min/1.73 m^2
- Stage 4: severe CKD with GFR 29–15 mL/min/1.73 m^2
- Stage 5: CKD with GFR < 15 mL/min/1.73 m^2, or where patient survival depends on provision of RRT in the form of dialysis or transplant.

potential advantages are challenges associated with ascertaining the cause of CKD, especially in primary care. The addition of albuminuria to the definition has substantial benefits for prognostication and will undoubtedly enhance the utility of the new scheme.

The evolution of these classification schemes over the last decade reflects our more refined understanding of CKD epidemiology. This trend is likely to continue in the future with identification of better markers for CKD and refinement in molecular diagnostic techniques.

Although less sensitive than definitions based on SCr or eGFR, ICD-9-CM codes have been used to classify CKD (Anonymous, 2005) (Box 1.2), with modifications in 2005 to reflect the NKF-KDOQI classification system.

Table 1.4 KDIGO Classification of CKD 2012 (Stevens et al 2013; Anonymous 2013)

Category	GFR, mL/min 1.73 m^2	AER mg/d	ACR Equivalent, mg/g	Descriptor
GFR		–	–	
G1	≥90	–	–	Normal or high
G2	60–89	–	–	Mildly decreased*†
G3a	45–59	–	–	Mildly to moderately decreased
G3b	30–44	–	–	Moderately to severely decreased
G4	15–29	–	–	Severely decreased
G5	<15	–	–	Kidney failure
Albumlnuela				
A1	–	<30	<30	Normal to mildly increased
A2	–	30–33	30–300	Moderately increased*
A3	–	>300	>300	Severely increased‡

ACR = albumin-creatinine ratio; AER = albumin excretion rate; GFR = glomerular filtration rate.

* Relative to young adult level.

† In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for chornic kidney disease.

‡ Includeing the nephrotic syndrome (AER usually >2200 mg/d [ACR >2220 mg/g])

Modified by NT 7th Aug 2015

(Note that the other table on the page submitted with proof corrections was unchanged table 1.5 - NT)

Table 1.5 Classification[a] of CKD based on presence or absence of systemic disease and location within the kidney of pathologic anatomic findings

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative GN; focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fa bry disease	Renal dysplasia, medullary cystic disease, podocytopathies

ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease, GN, glomerulonephritis

Genetic diseases are not considered separately because some diseases in each category are now recognized as having genetic determinants.

[a] Note that there are many different ways in which to classify CKD. This method of separating systemic diseases and primary kidney diseases is only one, proposed by the Work Group, to aid in the conceptual approach.

Definition of CKD stage 5 and ESRD

CKD stage 5 is defined by eGFR < 15 mL/min/1.73 m^2 with or without RRT, while the term 'ESRD' connotes kidney failure, where dialysis or kidney transplantation is required to sustain life

Box 1.2 Clinical modification of ICD-9 (ICD-9-CM) staging for CKD

- 585.1: chronic kidney disease, stage 1
- 585.2: chronic kidney disease, stage 2 (mild)
- 585.3: chronic kidney disease, stage 3 (moderate)
- 585.4: chronic kidney disease, stage 4 (severe)
- 585.5: chronic kidney disease, stage 5
- 585.6: end-stage renal disease
- 585.9: chronic kidney disease, unspecified.

(Levey et al., 2011). CKD stage 5 and ESRD are therefore not synonymous because not all patients with CKD stage 5 receive RRT, some patients with asymptomatic stage 4 CKD (GFR 15–29.9 mL/min/1.73 m^2) may receive RRT, and kidney transplant recipients often have an eGFR > 15 mL/min/1.73 m^2. Most available data on the epidemiology of ESRD are derived from registries of patients receiving chronic RRT. Because of different access to RRT across regions and healthcare systems, the incidence and prevalence of ESRD may not be fully captured by renal registries, which actually focus on 'receipt of RRT' (discussed below).

Pitfalls and limitations of the definition/staging system for CKD

The NKF-KDOQI classification scheme has been widely adopted around the world (Eckardt et al., 2009; Ikizler, 2009; Gansevoort and de Jong, 2010). This important initiative permitted a common nomenclature for clinicians and researchers, and facilitated an international effort to educate the public about the significance of CKD. Despite these benefits, the scheme also has limitations. For example, individuals with only minimal functional or radiological abnormalities might be classified with stage 1 CKD despite the uncertain clinical relevance of these findings; elderly individuals with only mild reductions in eGFR could be classified as having stage 3 CKD—raising concerns about inappropriate labelling of healthy individuals as diseased (Chen and Hsu, 2003). Moreover, the prognosis of earlier stage disease is not necessarily better than those with more advanced stages, and progression from lower to higher stages is not necessarily inevitable. In fact, little is known about the natural history of stages 1 and 2 CKD and increasing evidence is accruing that a substantial proportion of patients with stages 3 and 4 CKD have stable eGFR (Keith et al., 2004).

It has been suggested as more appropriate to divide patients into those with certain urinary abnormalities such as isolated haematuria or microalbuminuria and those with impaired kidney function (Winearls and Glassock, 2009). The latter may warrant subclassifications based on the presence or absence of progression and associated risk factors such as hypertension and proteinuria (Glassock and Winearls, 2008a; Winearls and Glassock, 2009). Guidelines from the United Kingdom by the National Institute for Health and Care Excellence (NICE) have attempted to address some of these criticisms by dividing CKD stage 3 into 3A and 3B (eGFR of 45–59 and 30–55 respectively), and the addition of the suffix 'p' to CKD stages to denotes significant proteinuria (Anonymous, 2007). These issues have been the subject of vigorous debate in recent years (Levey et al., 2011), and revision to the NKF-KDOQI scheme by an international KDIGO working group has recently been published (Anonymous, 2013).

Risk factors and causes for CKD

A large body of epidemiological and clinical evidence has linked certain risk factors to the initiation and progression of CKD. These can be classified into distinct categories based on the presence or absence of established causation; factors that have been proven to be causal (risk factors) and those that are associated with CKD in the absence of established causal relationship (risk markers) (Anonymous, 2002; Levey et al., 2011).

Causes of CKD include diabetes mellitus, hypertension, ischaemia, infection, obstruction, toxins, and autoimmune and infiltrative diseases (Anonymous, 2002; Levey et al., 2011). Although it is important to identify the cause(s) of CKD so that specific therapy can be instituted, adverse outcomes (including cardiovascular events and progression to ESRD) often occur despite appropriate treatment and irrespective of the underlying cause (Levey et al., 2011).

Risk factors for development of CKD have traditionally been classified as susceptibility factors and initiation factors. Susceptibility factors increase susceptibility to CKD, for example, older age, male gender, and familial/genetic predisposition. Initiation factors directly initiate kidney damage; such factors include diabetes, hypertension, chronic infections, drugs, and toxins. The progression factors are risk factors associated with worsening of already established kidney damage, such as high levels of proteinuria, hypertension, poor glycaemic control in diabetes, obesity, and smoking (Anonymous, 2002, 2007; Levey et al., 2011). However, the difficulty of detecting the early stages of CKD makes it difficult to determine whether the risk factors so far identified in the population relate more to susceptibility, initiation, or even progression. Therefore, this traditional classification may be somewhat artificial. These risk factors may also be subclassified as potentially modifiable/preventable and non-modifiable (Table 1.6). Finally, risk factors can also be classified as clinical (diabetes, hypertension, autoimmune diseases, systemic infections, drugs) or sociodemographic (age, race, poverty/low income, toxins).

Global CKD epidemiology

Initial population-based estimates of the prevalence of CKD were obtained from the National Health and Nutrition Examination Survey (NHANES) in the United States. The prevalence of eGFR <60 mL/min/1.73 m^2 in the NHANES 1999–2004 survey was 8.4%, the prevalence of microalbuminuria was 9.8%, and prevalence of overall CKD stages 1–4 was 10.0% (Coresh et al., 2003). The prevalence of CKD in the United States has increased by about 3% since the 1980s, possibly due to epidemiological transition with ageing population and the increasing burden of diabetes and hypertension (Levey et al., 2011). For instance, the prevalence of CKD in the United States in 1999–2004 was reported to be higher than it was in 1988–1994 (Coresh et al., 2007).

Table 1.6 Risk factors for CKD in the general population

Non-modifiable factors	Potentially modifiable or preventable factors
Older age	Systemic hypertension
Gender	Diabetes mellitus
Race/ethnicity	Cardiovascular disease
Familial/genetics	Dyslipidaemia
	Smoking
	Obesity/metabolic syndrome
	Alcohol consumption
	Low socioeconomic status
	Infections/infestations
	Drugs and herbs/analgesic abuse
	Obstructive uropathy/stones

CKD = chronic kidney disease.

Table 1.7 Representative population-based studies of CKD

Reference	Study	Design	N	Outcome	Target	Alb/Prot (%)	GFR < 60 mL/min/1.73 m^2 (%)
North America							
Brown et al., 2003	KEEP	CS/L	11,246	Prot, Alb, CKD	HR	MA = 27	16
Coresh et al., 2003	NHANES	CS/L	15, 626	Prot, Alb, CKD	GP	MA = 6.3	4.3
Garg et al., 2004	Elderly in LTCF	CS	9931	CKD	HR	–	35.7 (overall), 27.1 (M), 38.8 (F)
Rosas et al., 2005	Mexican Health Survey	CS	46, 523	Prot	GP, Hispanic	Prot = 9.2	–
Scavini et al., 2007	Zuni Kidney Project	CS	1483	Alb	HR	DM: MA = 34 Non-DM: MA = 11.1	–
Australia and Oceania							
McDonald et al., 2003	Tiwi Aborigines	CS/L	237	CKD; Alb/Prot	HR	Prot = 2.4; Alb = 44.0	12
Atkins et al., 2005	AUSDIAB	CS	11,247	Alb	GP	MA = 6.0; Prot = 0.6	–
Asia							
Ramirez et al., 2003	NKF	CS/L	450,000	–	GP/HR	Prot = 0.8–5	–
Li et al., 2005	SHARE	CS	1811	–	GP	Prot = 3.2	–
Choi et al., 2006	Kangbuk Samsung	CS	4883	–	GP	MA = 5.4 (overall)	–
Konta et al., 2006	Takahata	CS	2321	–	GP	MA = 13.7	28.8
Zhang et al., 2007	Beijing	CS	2353	–	GP	Alb = 6.2	–
Abo-Zenah et al., 2008	Saudi-Arabia	CS	2000	–	Army recruits	Alb = 6.2	–
Europe							
Jensen et al., 1993	Copenhagen City Heart Study	CS	1011	–	GP	MA = 3	–
Cirillo et al., 1998	Gubbio	CS	1567	–	GP	MA = 5–11	–
Liese et al., 2001	MONICA/ AUSBURG	CS	2136	–	GP	MA = 8 (M), 7.5 (F)	–
Hillege et al., 2002	PREVEND	CS/L	40,000	–	GP	MA = 7 (overall)	–
Romundstad et al., 2002	HUNT	CS	65, 258	–	GP/HR	MA in DM = 27.8; in HT = 19.38; in non-DM/HT = 5.2	–
Otero et al., 2005	EPIRCE	CS	237	–	GP	MA = 7.6	5.1 (overall)
Vitkorsdottir et al., 2005	ICELAND	CS	19, 381	–	GP	Prot = 2.4 (M), 0.9 (F)	4.7 (M), 11.6 (F)
Nitsch et al., 2006	SAPALDIA	CS	6317	–	GP	–	13 (M), 36 (F)

Alb = albuminuria; AUSDIAB = Australian Diabetes, Obesity and Lifestyle study; CKD = chronic kidney disease; CS = cross-sectional; DM = diabetes mellitus; F = female; GFR = glomerular filtration rate; GP = general population; HR = high risk; KEEP = Kidney Early Evaluation Programme; L = longitudinal; LTCF = long-term care facility; M = male; MA = microalbuminuria; N = number; NHANES = National Health and Nutrition Evaluation Survey; NKF = National Kidney Foundation; PREVEND = Prevention of Endstage Renal and Vascular Disease; Prot = proteinuria; SHARE = Screening for Hong Kong Asymptomatic Renal Population and Evaluation Programme; SAPALDIA = the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults.

Since the publication of the NHANES III results in the United States, many other studies were conducted in Australia, Europe, Asia, and North America based on these initial observations; a representative but not systematic selection is presented in the Table 1.7 (reviewed in Zhang and Rothenbacher, 2008). These studies are population based, and often focus on the general population—although some performed targeted screening of high-risk individuals. Most studies relied on dipstick urine testing for albuminuria estimation and/or measurement of SCr in conjunction with estimation of creatinine clearance or GFR using the Cockcroft–Gault or the Modification of Diet in Renal Disease (MDRD) 4-variable formulae (Zhang and Rothenbacher, 2008). The prevalence of microalbuminuria in these studies varies between 3% and 16%; the prevalence of stages 3–4 CKD ranges from 2.5% to 4%; and the prevalence of ESRD and stage 5 CKD are markedly lower (0.1 and 0.3%, respectively). This sharply reduced prevalence

of more advanced disease may reflect lack of progression from stage 3 and 4 to stage 5, or possibly competing risk from cardiovascular disease and mortality (Adler et al., 2003; Keith et al., 2004; Tonelli et al., 2006).

Of note, the prevalence of CKD depends on the incidence of CKD as well as the duration of CKD, which in turn reflects transition between stages of CKD and survival. Some insight can be gained from a large longitudinal study on CKD outcomes from the United States (Keith et al., 2004)—which showed that only 3.1% of patients with stage 2 through stage 4 disease progressed to RRT, while 24.9% died. Thus, death was far more common than dialysis among community-dwelling people with mild to severe CKD.

These studies have substantially advanced our understanding of the epidemiology of CKD. However, some people with reduced eGFR on a single measure may have normal kidney function on recheck—as reflected by current recommendations suggesting at least two measures that are 3 or more months apart—so prevalence might have been overestimated in some studies that used only a single measure of eGFR (Glassock and Winearls, 2008b; Winearls and Glassock, 2009). Also, concern has been expressed regarding the suitability of albuminuria and the use of the MDRD formula for calculation of eGFR in the general population. Of note, small amounts of albuminuria are not a specific manifestation of kidney disease, since it can occur in a number of inflammatory conditions and is often transient. The latter does not accurately estimate GFR when true GFR is > 60 mL/min (Glassock and Winearls, 2008a). Some of these limitations are being addressed with development of more accurate and precise estimating equations—for instance, the CKD Epidemiology Collaboration (CKD-EPI) equation performs better at higher true GFR, and leads to slightly lower population-based estimates of CKD prevalence. For example, using the CKD-EPI equation rather than the MDRD equation reduced the estimated prevalence of CKD in the United States to 11.5% (95% confidence interval (CI), 10.6–12.4%) from 13.1% (CI, 12.1–14.0%) using the MDRD equation (Matsushita et al., 2010a; Stevens et al., 2010).

CKD in special populations

The epidemiology of CKD may differ in special populations such as ethnic minorities, aboriginal people, Roma, the homeless, and children (Esbjorner et al., 1997; Ardissino et al., 2003; Harambat et al., 2012)—perhaps due to differences in genetic, behavioural, and sociodemographic characteristics (Foster, 2008; Huong et al., 2009; Hoy et al., 2010). There have been several population-wide surveys on the prevalence of CKD in indigenous people particularly in Australia and Canada (Gao et al., 2007; Hoy et al., 2010). Aboriginal people tend to have a higher burden of CKD than found in the general population (Katz et al., 2006; Gao et al., 2007; Hoy et al., 2010). For instance, on a remote Aboriginal island community, 26% of adults had microalbuminuria and 24% had overt albuminuria when screened in 1992–1995 (Hoy et al., 1998).

Data on CKD epidemiology among ethnic black people is predominantly US based (KEEP, 2002) and information about the incidence and prevalence of CKD in Africa is sparse. In both the United States and the few communities in Africa where studies were conducted, black people tend to have a higher burden of CKD than white people. For instance, in a community survey conducted in adults attending primary care clinics in Soweto, 35% of the people screened had proteinuria; 10% needed referral to a tertiary hospital, and of these, most had stages 3–5 CKD (Katz et al., 2006). A recent conservative estimate on prevalence of CKD in a sub-Saharan African country was 36% (Sumaili et al., 2009), as compared to 13.1% in the United States (Coresh et al., 2007).

CKD screening: measures and utility

Currently, screening for CKD is accepted practice only in people with hypertension or diabetes (Anonymous, 2002). The UK CKD guidelines also recommend at least annual screening of all adults at risk of obstructive kidney disease and those with prevalent CVD, while the US KDOQI guidelines extend screening to all those aged > 60 years with testing for albuminuria (using urine albumin/protein), SCr, and estimation of GFR (Anonymous, 2002, 2007). Recommendations from the ISN are more liberal, and advocate proactive screening for markers of CKD in all subjects visiting general practitioners, similar to the screening for high blood pressure or cholesterol concentrations (Levey et al., 2011). However, all these recommendations are based mostly on expert consensus rather than high quality evidence, and doubt remains as to whether population or targeted screening is justifiable and cost-effective (Boulware et al., 2003; Manns et al., 2010). In cardiovascular disease (CVD), it has been argued that population screening would be more effective than targeted approaches as most cases are not derived from the minority at highest risk (Levin and Stevens, 2011). However, CVD is more prevalent than CKD, and it is uncertain whether the same arguments apply. Before population-based screening for CKD could be recommended, further research is required to determine the true prevalence of early stages of CKD in different populations; the prevalence of associated risk factors; the attributable risk associated with such risk factors; their amenability to treatment; and the incremental benefit compared to case-finding by means other than organized screening.

Prognosis and outcome in CKD

Overall, even a mild reduction in estimated eGFR is associated with adverse clinical outcomes, as is increased urinary protein excretion (reviewed in (Matsushita et al., 2010b; Gansevoort et al., 2011; van der Velde et al., 2011). Among subjects with normal kidney function, proteinuria is independently associated with an increased risk of poor outcomes, which is further amplified in the setting of reduced eGFR—and has been observed in multiple populations including those at high CVD risk (Gerstein et al., 2001; Mann et al., 2001; Rahman et al., 2006; Solomon et al., 2007; Yokoyama et al., 2008; Anand et al., 2009) and in the general population (Grimm et al., 1997; Clausen et al., 2001; Kasiske, 2001; Hillege et al., 2002; Go et al., 2004; Klausen et al., 2004; Tonelli et al., 2006; Hemmelgarn et al., 2010; Matsushita et al., 2010b).

Epidemiology of renal replacement therapy

Definition of RRT

(See Sections 12 and 13.)

RRT comprises the different forms of haemodialysis, peritoneal dialysis, and kidney transplantation and may be used to overcome a short period of kidney failure. The majority of RRT patients, however, receive chronic RRT for the treatment of ESRD (Levey et al., 2011). As mentioned earlier, not all patients with ESRD receive RRT—for example, due to differences in access to RRT across healthcare systems, or because of cultural differences in referral

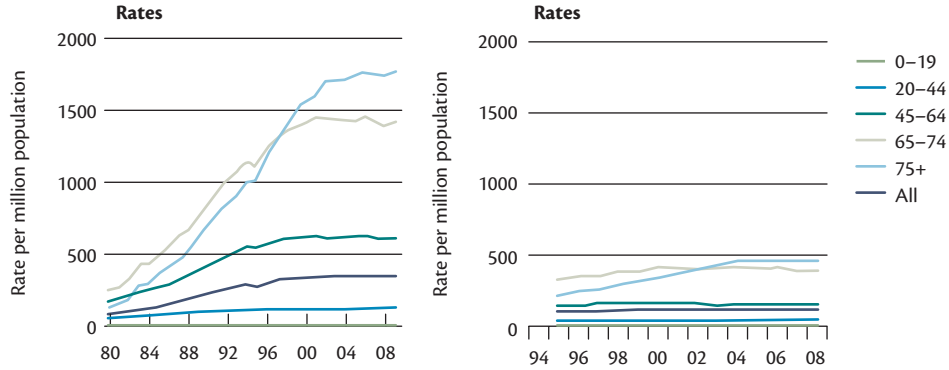

Fig. 1.4 Incidence of RRT by age category in USRDS (left) and ERA-EDTA registry (right) 1998–2012 (ERA-EDTA Registry, 2014; US Renal Data System, 2014).

patterns and patient attitudes towards RRT. Therefore, estimates based on the incidence and prevalence of chronic RRT will underestimate the burden of ESRD.

Risk factors and causes of ESRD

Risk factors for ESRD are similar to those for CKD—with the caveat that characteristics that reduce the risk of mortality may also increase the risk of ESRD (since only those who survive long enough can receive RRT). Worldwide, diabetes mellitus and hypertension are the leading causes of ESRD treated with RRT.

Renal registries use different systems for coding primary renal diseases underlying ESRD. The US Renal Data System (USRDS) makes use of ICD-9-CM coding, other registries use ICD-10, but the majority make use of (modifications of) the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) coding system for primary renal diseases (van Dijk et al., 2001; Venkat-Raman et al., 2012).

Global epidemiology of RRT for ESRD

The incidence of RRT as reported by registries is determined by the age and sex distribution of the general population, the prevalence of diseases underlying ESRD, factors related to progression of CKD, survival from competing risk like CVD, access to RRT (Caskey et al., 2011), the timing of starting RRT in relation to GFR, and the completeness of data within those registries. The prevalence of RRT results from the incidence of RRT and the survival of RRT patients.

Registry data show substantial changes in the incidence rates of RRT over the last 15 years. Figs 1.4 and 1.5 provide examples of trends in the United States and in Europe by age and primary renal disease.

The initial rapid growth in incidence rates was likely due to a combination of population ageing, increased prevalence of diseases underlying ESRD, and an increased acceptance of older and sicker patients. In addition, a substantial rise of the number of patients starting dialysis above 10 mL/min/1.73m^2 has provided a significant contribution to this increase (Rosansky et al., 2009). Recent data indicate that in the United States and in Europe the incidence rate of RRT has decreased since 2009 (US Renal Data System, 2014; <http://www.era-edta-reg.org>). Current differences in the incidence of RRT across the world are striking (Table 1.8). Mexico, Taiwan, and the United States have the highest incidence rates, whereas Hungary, Portugal, and Greece rank first in Europe.

The prevalence of RRT has continued to increase by 1–2% per year (Kramer et al., 2009; US Renal Data System, 2014). Although in some countries this may in part be due to increased patient survival on RRT, the increase in prevalence may merely reflect higher numbers of patients starting RRT than numbers of patient deaths. Countries with the highest burden of RRT patients include Taiwan, Japan, and the United States.

In general, patients on RRT have an unfavourable prognosis with remaining life expectancies being reduced to 20–35% in dialysis patients and to 70–80% in transplant recipients (ERA-EDTA Registry, 2014; US Renal Data System, 2014). In dialysis patients both cardiovascular (Foley et al., 1998; de Jager et al., 2009) and non-cardiovascular (de Jager et al., 2009; Sarnak and Jaber, 2000) mortality are highly increased compared with those in the general population. Determinants of patient survival on RRT include age and sex, the cause of ESRD, timing of referral to a nephrologist, genetic factors, general population mortality, access to

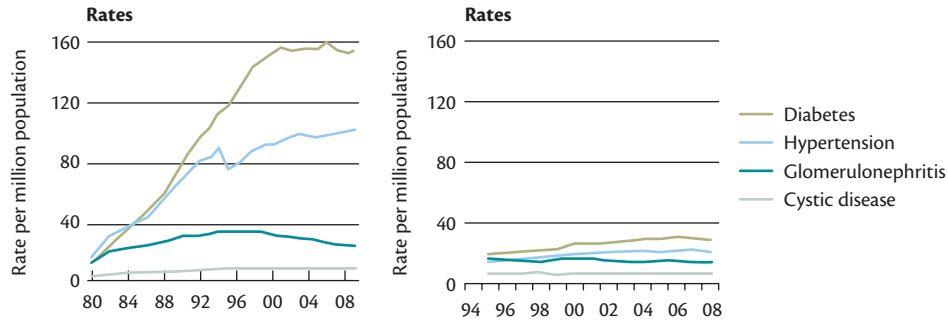

Fig. 1.5 Incidence of RRT by primary renal disease in USRDS (left) and ERA-EDTA registry (right) 1998–2012 (ERA-EDTA Registry, 2014; US Renal Data System, 2014).

Table 1.8 Incidence and prevalence estimates of RRT in different countries in 2012

Country	Incidence rate of RRT (pmp)	Incidence of DM (%)	Incidence of DM (pmp)	Prevalence of RRT (pmp)	Prevalence of RRT (pmp) on transplant	Prevalence of HD as % of dialysis)
Albania	67	10	7	325	73	
Argentina	159	36	57	836	168	95
Australia	112	36	40	916	411	81
Austria	140	26	36	1023	516	91
Bahrain	258	36	93	328	51	88
Belgium	188	20	37	1225	514	92
Bosnia and	125	29	36	718	52	96
Brazil	172			720	216	91
Canada	156	38	59	1183	500	83
Chile	170			1263	203	95
Croatia	158	24	38	1033	384	93
Denmark	124	28	35	872	411	80
Estonia	81	22	17	554	328	86
Finland	81	34	27	808	482	82
France	154	22	33	1139	507	93
Georgia	200	24	47	546	49	97
Greece	210	26	54	1136	231	93
Hong Kong	165	48	79	1192	484	27
Hungary	234	39	91	633		86
Iceland	59	0	0	683	440	73
Indonesia	191	26	50	265		96
Iran	105	22	23	621	299	95
Israel	183	49	89	1125	395	94
Japan	285	45	128	2365		97
Latvia	89	20	18	538	290	74
Malaysia	225	61	137	1056	64	91
Mexico (Jalisco)	467	59	276	1409	526	50
Montenegro	24	27	7	310	135	94
Netherlands	120	16	20	923	539	85
New Zealand	116	49	57	901	344	69
Norway	103	17	17	887	639	84
Oman	110	48	53	695	331	92
Philippines	117	44	51			95
Poland	135	25	34	748	254	94
Portugal	220	31	69	1670	602	93
Qatar	83			280	2	77
Rep. of Korea	221	51	113	1353	272	87
Romania	151	13	20	766	58	89
Russia	48	17	8	214	44	92

(continued)

Table 1.8 Continued

Country	Incidence rate of RRT (pmp)	Incidence of DM (%)	Incidence of DM (pmp)	Prevalence of RRT (pmp)	Prevalence of RRT (pmp) on transplant	Prevalence of HD as % of dialysis)
Saudi Arabia	126	39	49	730	245	91
Serbia	123	24	30	752	106	91
Singapore	285	66	188	1741	368	88
Slovenia	122	28	34	996	310	97
Spain	120	25	30	1092	555	89
Sweden	115	23	26	933	530	79
Taiwan	450	45	203	2902		90
Thailand	221	38	84	906	89	77
Ukraine	25	12	3	147	18	85
United States	359	44	159	1976	594	91
United Kingdom	107	24	25	867	435	86
Uruguay	150	33	40	1073	316	90

Sources: ERA-EDTA 2014 and USRDS 2014; where cells are empty, data are unavailable.

transplantation, and other aspects of quality of RRT care (Kramer et al., 2012).

There exists considerable international variation in the survival of patients starting dialysis (Kramer et al., 2012). Differences in patient age, sex, primary renal disease, and the presence of co-morbidities explain only a small part of that international variation (Goodkin et al., 2003; van Manen et al., 2007). Even when general population mortality rates and differences in treatment characteristics are taken into account, a major part of the variation in dialysis mortality across countries remains unexplained (van Dijk et al., 2007). Recent data suggest that the mortality of dialysis patients is higher in countries with high expenditure on healthcare. Complementary explanations for the international variation in mortality on dialysis may therefore include a more liberal acceptance policy among richer nations, differences in access to transplantation as well as different patterns of healthcare spending (Kramer et al., 2012).

RRT in special populations

(See Chapter 95.)

The epidemiology of RRT differs in specific populations like ethnic minorities and children.

Data from the USRDS (2014) show that in 2012 the age- and sex-adjusted incidence rates of RRT for African Americans, Native Americans, and Asians were 908, 412, and 379 pmp. This is 3.3, 1.5, and 1,4 times greater than the rate of 279 found in white people. Incidence rates from Europe, albeit lower, have shown an increased incidence rate of RRT in Asians and black people (Roderick et al., 1996) and in non-Caucasians in general (van den Beukel et al., 2010), whereas in Canada, Australia, and New-Zealand incidence rates are highly increased in indigenous people (Dyck, 2001; McDonald, 2010; McDonald et al., 2010). Increased incidence rates in ethnic minorities frequently come together with better patient survival rates. US and UK black patients (Roderick et al., 2009; US Renal Data System, 2014), UK South Asian (Roderick et al., 2009), and non-Caucasian Dutch RRT patients (van den Beukel et al., 2008) have better survival rates than their white and non-Caucasian counterparts. In contrast, in Aboriginal Australians and New Zealand Maoris patient survival is lower compared with that of non-indigenous people (McDonald and Russ, 2003). The background of these survival differences requires further elucidation.

In 2008, the median incidence rate of RRT in children aged 0–19 years was 9 (range 4–18) per million age-related population (pmarp) with the highest incidence rates in adolescents (Harambat et al., 2012). In children the pattern of diseases underlying ESRD is quite different from that in adults. In developed countries congenital disorders, including congenital anomalies of the kidney and urinary tract (CAKUT) and hereditary nephropathies, are responsible for more than half of all cases starting RRT. Differences in the incidence and causes of RRT across races and ethnic minorities are already reflected in paediatric populations (Harambat et al., 2012). The prevalence of RRT was around 65 pmarp in Australia, Canada, Malaysia, and Western-Europe, whereas the United States had a higher (85 pmarp) and Japan a lower (34 pmarp) prevalence. Although mortality of children on RRT is relatively low compared with that in adults (2-year survival 96% in Europe (ERA-EDTA Registry, 2014) and 95% in the United States (US Renal Data System, 2014), their risk of death is about 30 times higher than in their healthy peers (Groothoff et al., 2002; McDonald and Craig, 2004).

Future challenges

A key future challenge is to improve the definition and characterization of various kidney disease entities (Gansevoort and de Jong, 2010). This is an area of intense interest: better methods for SCr measurement, calibration, and standardization have evolved over the years, and higher-performance estimating equations are being developed (Stevens et al., 2010). In addition, newer filtration markers that are independent of muscle mass (such as cystatin C) are gaining increasing recognition and are being tested as a future alternative to SCr. Other potential biomarkers such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, monocyte

chemotactic peptide, netrin-1, and interleukin-18 among several others are becoming available for early identification of AKI (Waikar et al., 2008; Soni et al., 2011). It seems likely that some of these new tools will become more widely available, and will help to address the limitations of existing epidemiological studies. A second key challenge is to develop epidemiologic surveillance systems for both AKI and the various aspects of CKD—especially non-dialysis-dependent disease (Levey et al., 2011), and in developing nations (Barsoum, 2006; Nugent et al., 2011). Third, better information is needed on who to screen for kidney disease (as well as what test should be used and when screening should be performed)—aiming to identify people in whom early intervention to prevent adverse outcomes is feasible and cost-effective. These initiatives will help to establish the prevention and treatment of CKD as an important public health issue, and potentially as part of the WHO strategy on chronic non-communicable diseases (Couser and Riella, 2011).

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CHAPTER 2

Clinical assessment of the patient with renal disease: overview

Christopher G. Winearls

Introduction

The next chapters describe the presentations of renal diseases, their assessment from the history and physical examination, and their investigation by the use of laboratory tests, imaging, and histopathology.

Nephrologists are referred patients by their colleagues in primary care or in other specialties when they believe that there is a kidney problem needing an expert. That judgement is not always correct, for example, oedema or haematuria often have causes outside the kidney.

The reasons for referral are in three categories:

1. To explain abnormalities attributable to kidney disease that have been found in *asymptomatic individuals* including those at risk of familial conditions.
2. *Symptomatic renal disease*: renal failure, either acute or chronic; abnormalities of urination including poly- and oliguria, visible haematuria; unexplained loin pain; the classic renal syndromes (nephritic and nephrotic).
3. *Renal consequences of systemic conditions:* metabolic, inflammatory, infectious; drugs, malignancy, pregnancy, organ failure (especially cardiac and hepatic).

When responding to referrals coming by letter, telephone, or email there are two questions to be asked:

1. Should one be involved in this patent's care and if so how? In other words, will one be able to add value? The problems seldom come neatly packaged. They have often emerged into prominence in the context of complex other diseases, both acute and chronic. Sometimes the referral is for diagnosis, sometimes it is management, and sometimes it is both. These dilemmas are particularly poignant for nephrologists who have at their disposal two powerful tools. They can examine the diseased organ directly by examining tissue obtained by biopsy and can, theoretically, replace its function indefinitely. The question should sometimes be not, 'Can I?' but, 'Should I be involved?' It takes some courage to admit that one has nothing to offer, for example, the patient with oliguria and terminal heart failure or malignant disease. It is hubristic to suggest interventions directed at a consequence of irremediable disease which may prolong suffering for no more than a few days and delay a merciful death and so one should pause before doing so. The supplementary question is; 'If I should be involved, should I be the clinician in overall charge?' When the renal disease dominates the clinical problem, for example, in acute dialysis dependent renal failure, there are advantages in one team determining the priorities and supervising drug prescription. There are others in which a supportive role is sufficient. To take charge of every patient with a renal component to their illness would overwhelm the service. This is a particular problem in patients with renal failure as an additional complication of complicated surgery. Such patients need to be managed in the service responsible for treating the root cause. Without so doing, the renal problem will not resolve either.
2. How soon does one need to be involved? Contact may need to be immediate, for example, when there is an acute uraemic emergency or delayed as a routine outpatient assessment. This 'triaging' is not always straightforward. Some patients with life- and kidney-threatening conditions can appear deceptively well. Two examples come to mind—acute cast nephropathy in myeloma and rapidly progressive glomerulonephritis. One should not be deceived by the automatic labelling of a patient with an abnormal creatinine that has been translated into an estimated glomerular filtration rate (eGFR), as having chronic kidney disease usually abbreviated in correspondence to 'CKD'.

Having accepted the referral the nephrologist should clear his/her mind of the potentially misleading glib statements within referral letters and clinical notes, assumptions of the diagnosis, and the prejudices of the referrer or indeed the patient. Who has not seen the oedematous 'nephrotic' patient without proteinuria who actually has heart failure or the patient with a reduced eGFR labelled as having 'CKD' explained by anything from bodybuilding to hypothyroidism? A good rule is to assume that the referral lacks several pieces of highly relevant information and includes some that are actually wrong—'no nephrotoxic drugs', 'normal-sized kidneys', and 'no relevant family history' are common false assertions.

It is then time to apply the 'clinical method' which comprises the following steps:

- Identification of the *presenting complaint* and its immediate history. The history should be methodically retaken including the general *history* of the patient including past medical, drug, social, travel, illness in the family, and a systematic enquiry of the function of other systems.
- Performing a general physical *examination.*
- Arranging laboratory and imaging *investigations*—screening and targeted.

- Constructing a differential diagnosis.
- Formulating a plan for *management*: specific and general.
- *Communicating* the conclusions to the patient, referring colleagues and others who will be needed to contribute to care.

There is no substitute for 'the clinical method'. It is a false economy to move straight to investigations not only because these may not provide the answer but because their interpretation will depend on the clinical context. Radiologists and renal pathologists rightly expect nephrologists to describe the problem and how the findings will alter management.

Accurate diagnosis is paramount for it informs the medical management exactly but knowing everything else will dictate how this will be delivered.

The way the clinical method is applied depends on the clinical presentation—these are described in Chapter 3.

CHAPTER 3

Presentations of renal disease

Christopher G. Winearls

Introduction

It is not patients who seek the advice and help of nephrologists but primary care physicians and medical and surgical colleagues, who have identified a problem that they believe calls for the expertise of a nephrologist. What are these circumstances?

Abnormalities in asymptomatic patients raising the suspicion of renal disease

The referral usually follows the finding of an abnormality on clinical or laboratory examination that is not causing symptoms. These arise at routine medical examinations at school, for employment, military service, life and salary insurance, immigration, major surgery, potential live kidney donation, registration with a new family doctor, 'well woman/man' clinics and as part of health screening in at-risk individuals with systemic disease, at booking for pregnancy care, and assessment of the risks of methods of contraception. The potential for causing anxiety is significant, especially if the patient attends a renal unit for evaluation, walking past signs to the dialysis and transplant wards. This concern has to be balanced against the wish to make an early diagnosis of renal disease in case it is possible to halt it, delay its progress, and defer or prevent the onset of renal failure. We will consider first the common reasons patients are referred to a nephrologist for the first time.

Abnormal findings in patients at risk of renal disease and complications

Many referrals will come from colleagues in other disciplines who are on the lookout for renal problems associated with the condition they are treating or monitoring. Indeed they will have been advised to measure the estimated glomerular filtration rate (eGFR) more or less frequently.

- *Primary care physicians* are encouraged to screen for renal dysfunction in patients with diabetes, hypertension, heart failure, and vascular disease (ischaemic heart disease, strokes, and peripheral vascular insufficiency) and those on long-term treatment with drugs known to cause kidney injury, for example, lithium, non-steroidal anti-inflammatory drug, and calcineurin inhibitors.
- *Urologists* will refer patients with neurogenic bladders, urinary diversion, kidney stones, retroperitoneal fibrosis, and even relieved obstruction.
- *Gastroenterologists* will refer patients with malabsorption who are prone to oxalate nephropathy, and those on 5-aminosalicylic acid drugs used for inflammatory bowel disease which can cause interstitial nephritis at any time after they are instituted.
- *Cardiologists and vascular surgeons* will refer patients with atherosclerotic disease and abdominal aortic aneurysms may also suffer from renal vascular disease which comes to light when renin–angiotensin–aldosterone system (RAAS) blockade is instituted.
- *Haematologists* will refer patients with paraprotein disorders.
- *Rheumatologists* will refer patients with vasculitides in whom they are suspicious of relapse in the hope that a renal biopsy will confirm this and justify escalation of immunosuppression.
- *Radiologists* will often add as addendum to their reports of incidental findings of renal cysts, kidney size asymmetry, and parenchymal calcification, 'suggest referral to a nephrologist'.

Invisible haematuria (microscopic haematuria)

(See Chapter 46.)

This is by definition asymptomatic and is found when urine is tested with urine dipsticks as part of clinical assessment. This problem is not referred to nephrologists in the first instance.

Asymptomatic proteinuria

(See Chapter 50.)

This may have been detected by dipstick testing either as a part of a routine assessment or under abnormal conditions, for example, an intercurrent illness. Dipsticks can be misleading because they are not calibrated for urinary concentration. An early morning spot urine protein or albumin creatinine concentration should be requested and the presence of orthostatic proteinuria excluded before the patient is formally referred. The threshold for full evaluation of significant proteinuria (defined as > 300 mg/day or 30 mg/mmol creatinine) up to and including renal biopsy will depend on the clinical context and the 'need to know'.

Abnormal constituents of urine

(See Chapter 175.)

These include asymptomatic bacteriuria, and leucocyturia (see Chapter 175). Asymptomatic bacteriuria without leucocyturia suggests sample contamination, with leucocytes, an asymptomatic infection or urinary tract colonization. Isolated leucocyturia is found after treatment for an infection, in subjects with renal stones, interstitial nephritis, renal tuberculosis, or papillary necrosis.

An 'abnormal' eGFR

(See Chapter 94.)

This has become one of the most common reasons for referral to a nephrologist. This has arisen from the application of the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology

Collaboration eGFR equations to routine plasma creatinine measurements which are then reported as an eGFR and an interpretation as to a possible stage of chronic kidney disease (CKD), for example, 'an eGFR of 45–59 mL/min/1.73m^2 indicates stage 3A kidney disease'. Such statements are neither useful nor legitimate not least because a diagnosis of CKD requires the abnormal GFR to have been present for at least 3 months but also because the explanation may be acute kidney injury (AKI). It is also misleading because an eGFR of > 60 mL/min/1.73m^2 is not necessarily 'normal'. Indeed, there is no definition of a normal eGFR. Although an eGFR of < 60 mL/min is likely to indicate impairment of kidney function across the age range, the significance is different in the young compared to the old. A decision as to whether individuals with a reduced eGFR need a formal nephrological assessment will depend on their underlying co-morbid conditions, age, and the rate of change. The new KDIGO CKD guideline has the explicit requirement that CKD should be described according to cause, GFR, and albumin excretion—the CGA system (see Chapter 94). When the GFR is unequivocally abnormal (< 45mL/min/1.73m^2) or lower than predicted for the age of the patient there will need to be a decision on the urgency of the assessment. These dilemmas are explored and recommendations made in the KDIGO clinical practice guideline (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

A raised blood pressure

Patients are referred if there are indications that this may be secondary to renal disease (reduced eGFR, haematuria, and or proteinuria). They will require a full nephrological assessment. (See Chapter 210.)

Screening for an inherited disorder known to be present in the family

Common examples include autosomal dominant polycystic kidney disease (ADPKD), Alport syndrome, reflux nephropathy, urate nephropathy, and nephronophthisis-medullary cystic disease complex. (See Sections 15, 16.)

Incidental electrolyte abnormalities

(See Section 2.)

Hypokalaemia (K^+ < 3.5 mmol /L)

(See Chapter 34.)

This will often cause concern. When associated with hypertension, a number of disorders will have to be considered. These include renovascular hypertension and Cushing, Conn, and rarely Liddle syndromes. If the blood pressure is normal the simple explanations should be considered first, for example, thiazide and loop diuretic use, diarrhoea, and purgative use. The abuse of such drugs can be hard to prove. A rare explanation is spurious hypokalaemia caused by delay in potassium (K^+) measurement in patients with a membrane pump abnormality. This is also seen in patients with acute myeloblastic leukaemia. All these may have been excluded before the nephrologist is asked to confirm or deny the presence of Gitelman or Bartter syndromes.

Hyperkalaemia (K^+ > 5.5 mmol/L)

(See Chapter 34.)

This also causes concern and the risk-averse doctor will refer patients to hospital urgently for further blood tests. The explanations range from the trivial, a haemolysed or old blood sample especially if taken with a rare tight tourniquet, to the relevant, for example, a consequence of RAAS blockade with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), or potassium-sparing diuretics such as spironolactone or amiloride. This is becoming a common problem in patients receiving such combinations as part of their treatment for heart failure. When renal function is relatively preserved, these abnormal K^+ concentrations, usually approximately 6.5 mmol/L do not cause problems.

Hyper- and hyponatraemia

(See Chapters 28 and 29.)

Hypernatraemia is seldom asymptomatic but hyponatraemia (sodium < 135 mmol/L) often is. This is usually a consequence of salt wasting with mainly water replenishment, psychogenic polydipsia, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) a full description of this problem is provided in Chapter 28.

Symptomatic urinary disease

The patient has symptoms and signs that strongly suggest an underlying kidney or urinary tract disease. Patients in this group of referrals may be suffering urinary symptoms or from one of the recognized renal syndromes that trigger automatic referral to a nephrologist. These are listed in Table 3.1.

Urinary symptoms

Patients with problems of urination (micturition) are not referred to nephrologists in the first instance but these may be relevant in cases referred with haematuria, recurrent urinary tract infection.

Such patients will be referred either in the hospital setting or as requests for advice from the primary care. There is often overlap with urology and choice and direction of the referral is often perverse and random.

Table 3.1 Urinary syndromes and symptoms

Syndrome	Definition
Nephrotic	Oedema associated with hypoalbuminaemia and heavy proteinuria (usually > 3 g/day)
Nephritic	Hypertension and oedema associated with haematuria and proteinuria
Acute kidney injury	This is based on urine output and change in plasma creatinine concentration (Ftouh et al., 2013)
Chronic kidney disease	Abnormalities of kidney structure or function present for > 3 months with implications for health.
Chronic kidney failure	An eGFR < 15 mL/min causing uraemia requiring symptom control, dialysis, and or renal transplantation
Symptoms:	
Urinary symptoms	
Recurrent macroscopic haematuria	
Loin pain ± haematuria	
Hypertensive renal disease	
Dysuria, polyuria	

Dysuria

This is an umbrella term covering different sensations of discomfort with micturition and experienced, therefore, several times a day.

In men, burning in the penile urethra suggests urethritis but a deeper pain suggests problems in the prostate or bladder. If there are systemic symptoms and signs, the prostate should be considered and samples taken after prostatic massage and imaging organized. Acute prostatitis can progress to septicaemia and the treatment is different from cystitis. Cystitis is uncommon in men unless there is an underlying structural or predisposing cause such as a stone, outflow obstruction, or malignancy.

In women, dysuria is often associated with urinary urgency and frequency suggesting a diagnosis of cystitis. This occurs more commonly in women during their sexually active years but also after menopause when the effects of oestrogen deficiency reduce the defences of the bladder.

Dysuria also describes difficulty in actually passing urine. This is more common in men who will describe a collection of distressing symptoms pointing to bladder outflow obstruction. Because bladder emptying is incomplete, they notice frequency, including nocturia, urgency, difficulty in initiating micturition (waiting up to a minute for flow to start), a poor stream, and then dribbling after micturition is thought to be finished. The finding of a full bladder often palpable to the umbilicus, a large volume of post-micturition residual urine, and a thick-walled bladder on bladder scan give the diagnosis. The causes include urethral structure and prostatic occlusion of the urethra. This diagnosis is often made when these men, often elderly, are referred unexamined with 'CKD'. Strangury is the symptom of very painful and difficult micturition often caused by a bladder stone at the internal urethral meatus or in the urethra itself.

Urinary frequency, polyuria, and nocturia

It is essential to establish what the patient actually means when they describe 'Having to go to the toilet all the time'. 'How often and how much urine?' are the questions that need answering. It is best to get a record of a day's worth of micturition, charting time and volumes passed. A kitchen measuring jug will suffice. Frequent large volumes of urine point to a concentration defect and frequent small volumes to a micturition problem or bladder irritation or a contracted bladder volume, setting off detrusor contraction despite the presence of relatively small volumes.

The causes of true polyuria > 3 L/day are many (see Table 3.2). The diuresis may be the result of excess water consumption (polydipsia), obligate loss caused by solutes such as glucose, or failure of 'antidiuresis' at a central (posterior pituitary) or peripheral (the kidney) level. These are simply distinguished by direct questioning and occasionally a water deprivation test with and without administration of arginine vasopressin.

Table 3.2 Causes of polyuria

Cause	Diagnosis
Primary polydipsia	History and/or water deprivation
Solute diuresis	Urinary glucose
Drugs	Diuretic use
Central diabetic insipidus	Water deprivation test
Nephrogenic diabetes insipidus[a]	History, kidney imaging, and a water deprivation test

[a] Common causes: post-obstructive, hypercalcaemia, long-term lithium use or excess dose acutely, and many forms of interstitial kidney injury. (See Chapter 32.)

Primary or congenital diabetic insipidus is rare and will manifest in early life.

Nocturia is the disturbing need to wake and micturate during the sleep cycle. Provided the bladder has been emptied before retiring and fluids have been avoided in the preceding 1–2 hours, most healthy subjects can last until morning perhaps because sleep is associated with antidiuretic hormone (ADH) secretion. When the volumes of urine passed are low, the causes are those of frequency described earlier. Large volumes may be the continuation of the problem of polyuria but a reversed problem of micturition, that is, more at night than in the day is more problematic. It implies that there is more urine production at night than during the day and is attributed to preferential renal perfusion when the other calls on cardiac output are reduced. It is commonly seen in patients with CKD, congestive heart failure, and nephrotic syndrome.

Anuria and oliguria

(See Chapter 219.)

It is uncommon for patient to report these and curious that they do not notice that they have 'stopped going'. Anuria and oliguria (urine output < 400 mL/24 hours or < 0.5 mL/kg per hour) are emergencies and in the otherwise symptom free patient point to relatively few causes.

Anuria

The differential diagnosis includes acute renal vascular occlusion, catastrophic renal injury, for example, antiglomerular basement membrane (anti-GBM) disease, and bilateral complete urinary obstruction or obstruction of a single kidney.

Oliguria

There are many causes, including those of anuria, but there is usually evidence of a systemic disorder with or without a further aggravant or precipitant, for example, dehydration in a patient with heart failure and an ACEI and diuretics.

Both oliguria and anuria are observed in the hospital setting and will trigger an entry into an AKI algorithm examining prerenal, renal, and postrenal causes (Lameire et al., 2013).

Macroscopic haematuria

This is an alarming symptom and because of association of 'red' with danger, is seldom ignored. In the United Kingdom, any adult patient with painless macroscopic haematuria would be referred to a urologist to be seen within 2 weeks to exclude malignancy. Referral to a nephrologist is usually after the common urological causes have been excluded. The obvious 'medical' renal causes include ADPKD and over-anticoagulation but three glomerular diseases can manifest as macroscopic haematuria: Immunoglobulin A (IgA) nephropathy, Alport syndrome, and anti-GBM disease. Patients with the nephritic syndrome describe brown cloudy urine which is less alarming than truly bloody urine.

Loin pain

This problem is usually referred when a urological cause has already been sought but it is worth rehearsing the symptoms and causes associated with loin pain.

Renal colic is a very severe pain during which no normal activity can be undertaken. It is sudden in onset, comes in waves, radiates anteriorly and into the genitalia, and is associated with nausea and vomiting. It can abate quite suddenly. The urine will often but not always test positive for blood. This description implies that a stone or clot or papilla is in the ureter which is trying to move it on by peristalsis. These episodes are usually managed in the community and are only referred if the problem is recurrent or there are 'red flags'. These include fever (implying the possibility of infection behind an obstructing stone), known solitary kidney, pain resistant to standard analgesia, pregnancy, renal dysfunction, oliguria, or poor social support.

It is more difficult to attribute pain confined to the loin to the presence of a stone. There are other causes such as bleeds into renal cysts, pyelonephritis, renal infarcts, pelvi-ureteric junction obstruction, and the *loin pain haematuria syndrome*. This is a curious condition in which patients present with very severe chronic loin pain with and without visible haematuria and few if any abnormalities are found by imaging or even renal biopsy; the description of the pain is vivid and by the time of referral many patients are taking very large doses of opiate analgesics. Occasionally a factitious cause of haematuria is proved. On examination the patients are exquisitely tender during attempts to palpate the kidney bi-manually. There will often be a request for a surgical solution ranging from auto transplantation to nephrectomy. It is considered a form of somatoform pain disorder (Winearls and Bass, 1994) (See Chapter 47). Acute glomerulonephritis is occasionally associated with loin discomfort but seldom with severe pain. Severe loin pain has also been attributed to the 'nutcracker phenomenon' when the left renal vein is compressed between the aorta and the superior mesenteric artery.

Nephrotic syndrome

(See Chapters 48, 52.)

This is a shorthand term for the combination of oedema, heavy proteinuria, and hypoalbuminaemia. Cut-off concentrations as diagnostic criteria are unhelpful as there is a poor correlation with the effects of the syndrome. Hypercholesterolaemia is an epiphenomenon and not helpful diagnostically. Usually the plasma albumin is < 30 g/L, the urine protein loss > 3 g/24 hours or > 350 mg/mmol creatinine. The diagnosis may be missed if the latter two components are not sought and the oedema misattributed to immobility, heart failure, and venous insufficiency. Adult patients need prompt assessment by a nephrologist and almost all will require a renal biopsy. The cost of guessing the pathology by the known hierarchy of causes in age groups is too high to be allowed.

Nephritic syndrome

(See Chapter 46.)

This term describes the combination of oedema, hypertension, glomerular haematuria, and proteinuria (not in the 'nephrotic' range) with or without a reduction in GFR. A looser definition is glomerular haematuria with any of the features. Unlike the nephrotic syndrome the patient has evidence of a significantly expanded extracellular volume with a raised jugular venous pressure. This and the oedema are attributed to sodium and water retention caused by an acute inflammatory injury to the glomeruli. This is a classical complication of beta haemolytic streptococcal infection in children. It is rare in adults. The term is not much used today as most patients with this combination have recognized glomerular diseases such as IgA nephropathy, Henoch–Schönlein purpura (HSP), systemic lupus erythematosus (SLE) with a diffuse proliferative glomerulonephritis, or a systemic vasculitis.

Acute kidney injury

(See Section 11.)

AKI is defined as any of the following: an increase in serum creatinine by > 0.3 mg/dL (> 26.5 μmol/L) within 48 hours; or an increase in serum creatinine to > 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or a urine volume < 0.5 mL/kg/h for 6 hours (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). In practice, AKI covers a spectrum from transient minor to catastrophic kidney injury arising in both hospital and the community and always represents a nephrological emergency. There are two tasks: one is to attempt to halt or reverse the injury and the other is to provide support to the patient to compensate for the effects of renal failure (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012; Lameire et al., 2013).

Symptomatic chronic kidney disease

(See Section 5.)

The overt symptoms of chronic disease are usually late in the illness and deceptively non-specific. Once CKD or kidney failure have been found by the reporting of the eGFR the nephrologist has to decide whether these symptoms are indeed a consequence of the kidney disease. The lower the eGFR or more advanced the stage the more likely this is true. Patients with CKD stage 5 are almost always symptomatic though they often only acknowledge the severity after they have been dialysed, but those with CKD stage 3A and 3B are not.

At one extreme the symptom complex will include the full range of uraemic consequences affecting almost all systems:

- Dyspnoea is explained by pulmonary oedema, anaemia, and acidosis
- Anorexia and weight loss
- Pruritus
- Cognitive decline
- Sexual dysfunction by the central effects of the elusive uraemic toxins
- Skeletal discomfort and proximal weakness by secondary hyperparathyroidism

The patient has a systemic disorder known to be complicated by renal involvement

There are many conditions in which the kidney is the victim of collateral damage and this can be severe enough to mean that the nephrologist has to take responsibility for overall care.

Metabolic diseases and inherited disorders

(See Chapters 149, 167, 334.)

The most important is diabetes mellitus that is now the single most common cause of end-stage renal disease. CKD clinics

are now dominated by patients with earlier stages of diabetic nephropathy hoping that good conservative management will prevent or delay progression. Unfortunately many have passed beyond the point of reversibility so the major contribution of the nephrology clinic is in helping to find a tolerable and effective combination of blood pressure-lowering drugs. Tuberous sclerosis, sickle cell disease, and other rarer disorders such as Anderson–Fabry disease or cystinosis also cause renal failure and their care has to be shared with experts in their other manifestations.

Malignancy

(See Chapters 60, 63, 150, 172, 251.)

Apart from the obstructing effects of solid tumours on the renal tract there are non-metastatic effects such as membranous and membranoproliferative glomerulonephritis and hypercalcaemia. Chemotherapy with agents such as cisplatin has adverse effects on the kidney which if extreme make renal replacement necessary.

The tumour lysis syndrome is less common now that the risks have been recognized but still occurs in patients with high tumour burdens (especially leukaemias) responding to effective chemotherapy. This is a renal emergency requiring prolonged dialysis to control potassium, urate, and phosphate concentrations.

The most common joint malignancy-kidney problem is in paraprotein disorders the effects of which range from acute cast nephropathy to the deposition disorders such as AL amyloid, light- and heavy-chain deposition disease.

Infection

(See Sections 8 and 11.)

Sepsis and shock are the most common cause of AKI in the hospital setting but there are community acquired infections that present with life-threatening renal injury too. The best examples are falciparum malaria, *Escherichia coli* O157 causing haemolytic uraemic syndrome (HUS), leptospiral infection causing Weil disease, hantavirus infection, and post-infectious proliferative glomerulonephritis (usually a consequence of beta haemolytic streptococcal infection). Subacute and chronic infections can lead to glomerular injury too: hepatitis B and C, HIV, and bacterial endocarditis are the most common. Renal tuberculosis is quite rare in the developed world but not so in emerging economies.

Auto-immune inflammatory disorders

(See Chapters 156, 162, 165, 166.)

The management of the renal consequences of the vasculitides especially SLE, HSP, systemic sclerosis, the polyangiitides are a significant part of the acute and long-term workload of clinical nephrologists. Sarcoidosis and Sjögren syndrome can involve the kidney and evidence of interstitial inflammation obtained from renal biopsy provides justification for immunosuppressive treatment which is otherwise usually held in reserve.

Effects of drugs

(See Chapter 362.)

Most drugs are two-edged swords and the prescribers dread finding changes in renal function especially if they are uncertain as to whether the drug is really the cause. This is a particular problem in oncology (cisplatin and intravenous pamidronate), rheumatology, and infectious disease (antiretroviral and antituberculosis drugs, high-dose aciclovir and sulphonamides, and amphotericin are prime examples). Although drug withdrawal is an option, a definite diagnosis of the nature of the kidney injury is preferable. An allergic interstitial nephritis will require active treatment not just stopping the agent.

Pregnancy

(See Chapter 250.)

Pregnancy is a systemic state in which the kidneys are vulnerable especially if there is any underlying renal disease. The catastrophic effects of the later specific complications such as eclampsia, haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, and HUS almost always require nephrology input.

Other system failure

(See Chapters 247–9.)

Patients with the end stages of heart and liver failure are usually referred with oliguria, disproportionate plasma urea concentrations, and hyperkalaemia, all explained by a combination of the system failure and the valiant pharmacological attempts to ameliorate their condition with various diuretics, ACEIs, and spironolactone. They are usually hypotensive and the decision on whether to offer renal support is finely balanced, especially if the underlying cause is irremediable.

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CHAPTER 4

Kidney disease-focused history taking

Christopher G. Winearls

Introduction

Each referral must be approached with an open mind. No assumptions should be made and every statement should be checked. One should not believe or disbelieve what has been asserted.

The presenting complaint

This will usually be in the pick list described in Chapter 3.

One should start with the simple introduction, 'I have been asked to see you because [presenting complaint] but I would like to know what you believe to be the problem.'

What concerns the patient is not always what concerns the doctor. For example, a patient consults a primary care physician because of tiredness, and is found to be anaemic and have renal impairment. It is easy to accept this sequence as causes and effect but it is often not so. Ten per cent of the population have 'chronic kidney disease' (CKD) but a minority are anaemic so one has to dissect the problem not just agree with the proposition.

The history of the presenting complaint

This involves a detailed exploration of the onset, duration, progression, alleviating and aggravating features, and associated symptoms. This is well illustrated by the visible haematuria of mesangial immunoglobulin (Ig)-A disease which is of acute onset, painless, may follow an infection, and is of short duration. It is quite different from that of a bladder tumour. The patient's understanding of medical words should be explored. What do they mean by 'UTIs', cystitis, 'kidney pain', migraine, angina? The same applies to the phrases in the referral which will often include vague and often misleading terms such as chronic pyelonephritis, essential hypertension, and 'PET'.

The past medical history

One is greatly assisted by a good general practice record of attendances or the hospital notes which should be examined from the first page. The past history may come as a cryptic computer printout that has been assembled over years and passed from one family practitioner to another. Each should be asked about and the basis of the diagnosis confirmed. This needs to be exhaustive, with prompting because patients have variable memories and notions of what constitutes a significant medical problem, for example, diabetes may be considered a longstanding background nuisance rather than a relevant condition 'because I have had it for so long and it does not cause me any problem'. Childhood illnesses are particularly difficult as the adult patient will not be accompanied by a parent and may have 'grown out' of the problem. Reflux nephropathy is often suspected from the story of the individual being a sickly child, with frequent fevers, courses of antibiotics, or enuresis which eventually resolved. Every operation, every medication, every hospitalization should be recorded. In women the history of pregnancies can be very revealing, for example, proteinuria at booking or blood pressure concerns that do not fit pre-eclampsia. Men have fewer opportunistic medical assessments but findings at employment, insurance, or military service medicals are helpful.

The drug (medication) history

One is often informed of the currently prescribed drugs, not those that may have triggered the problem or exacerbated it and have been discontinued. Examples of the missing culprits include lithium for bipolar disorder; 5-aminosalicylic acid for ulcerative colitis; proton pump inhibitors; gold or penicillamine for rheumatoid arthritis; intravenous bisphosphonates for breast cancer; cisplatin; non-steroidal anti-inflammatories; angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs); and calcineurin inhibitors for non-transplant indications.

There is seldom mention of the 'over-the-counter' drugs but the referrer may be unaware of these so the patient should be quizzed. Perhaps the most notorious example of this problem is Chinese herbal remedies which contain aristolochic acid.

The family history

This is perhaps one of the most neglected elements of history taking, for doctors rely on the catch-all question, 'Do any diseases run in your family?' Instead one should ask about causes of death and disability in three generations. Adult polycystic kidney disease commonly declares itself because a parent is on renal replacement treatment but there are families in which the affected parent has died prematurely, has been estranged or has not yet been diagnosed.

The social history

Patients are quite surprised that one wants to know so much about their ethnicity, where they were born, where they have lived, where they have travelled, what work they have done, what their habits—personal, sexual, smoking, drug use illicit and recreational—are. These provide clues to disorders such as HIV-associated nephropathy, focal segmental glomerulosclerosis, Chinese herb nephropathy, renal tract tumours, and atherosclerotic renal arterial disease.

Of course serious renal disease, especially when renal replacement treatment is required, has far reaching implications. One has to explore employment, relationships and domestic arrangements.

The review of systems

This can be tedious and unrewarding especially if the patient is trying to be helpful and agrees that they do have symptom such as chest pain or breathlessness 'occasionally'. It is best to leave the question open allowing them to declare and describe a symptom spontaneously. 'How is your breathing?' is preferred to 'Do you ever get breathless?' This said, one does have to be quite direct on sensitive issues such as sexual function.

CHAPTER 5

Kidney disease-focused features on examination

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Introduction

This depends on the context and clinical presentation and the emphasis will be different too. Tell-tale signs are often unnoticed in the general examination of the eyes (lecithin cholesterol acyltransferase deficiency (LCAT) deficiency, Fabry disease, corneal calcification), the skin (vasculitis, Anderson–Fabry disease), the optic fundus (haemorrhages and exudates, papilloedema), and the hands (nail patella syndrome, splinter haemorrhages of SLE and subacute bacterial endocarditis) (see Figs 5.1 and 5.2).

In the cardiovascular system, one is most interested in the volume status (the pulse, jugular venous pressure, and presence of oedema and its extent); blood pressure measured accurately with the an appropriate-sized cuff (the patient rested and lying down for 10 minutes and then standing); the left ventricular (LV) impulse for signs of LV hypertrophy (LVH), murmurs, and a pericardial friction rub; and the peripheral pulses. In the *respiratory system* one is looking for pleural effusions, signs of chronic suppurative lung disease, and clues to bronchial malignancy. In the *abdomen* it is the prominence of the kidneys, the bladder, and the presence of renal bruits that one wants to record. Pelvic examination is not usually routine but the slightest hint of bladder outflow problems or obstruction requires an examination of the prostate or the uterine cervix. In the *nervous system* one is interested in cognitive function reflecting uraemia; peripheral neuropathy in uraemia and diabetes; and autonomic neuropathy in diabetes and AL amyloid.

Investigations

These will be arranged after the completion of the examination but there are general principles that need stating (see Chapters 6–18).

The rule is to start with the simple and avoid requesting a comprehensive and unselected set of blood tests, the results of which may be distract or be difficult to interpret.

Before the consultation ends, one will want to know what the urine dipsticks show, for example, haematuria, proteinuria, leucocytes, and nitrites, and, if appropriate, urine microscopy (see Chapter 6).

A full blood count and biochemical screen including calcium, phosphate, and liver enzymes, and a C-reactive protein are reasonable routine requests because they may provide a clue to common disorders that have rather non-specific symptoms or may be clinically silent.

Once the problem is described the investigations are directed very specifically at diagnosis and consequences. For example, if one is sure one is dealing with true chronic kidney disease (CKD) one wants imaging of the renal tract, a further estimate of GFR, urine protein quantification, an electrocardiogram and echocardiogram looking for LVH, and a parathyroid hormone test for evidence of mineral and bone disorder (MBD).

The consultation is closed with a description of the working diagnosis, the way it will be resolved but avoiding a description of specific treatments, unless generic or justifiable, or indeed prognosis. This is more often the business of the follow-up. It is wise to counsel patients about the risks of searching the Internet which can cause unnecessary anxiety. There are good informative websites to which patients can be referred, for example, the website of the Edinburgh Renal Unit (<http://www.edren.org/info>).

Specific consultations

The acute uraemic emergency

(See Chapter 222.)

In the hospital setting, the nephrologist will usually be consulted either because the diagnosis is obscure or there is a need for renal replacement treatment. This will need to be instituted urgently if there are any of the life-threatening consequences of renal failure: pulmonary oedema, metabolic acidosis, hyperkalaemia, and encephalopathy. The same rules apply to community-referred patient after which the diagnostic algorithm is followed seeking prerenal, renal, and postrenal causes. As emphasized earlier, the clinical method takes precedence over investigation especially as physical examination is not usually diagnostic. Laboratory tests tend to be confirmatory rather than immediately diagnostic except in the silent renal diseases such cast nephropathy and anti-glomerular basement membrane (GBM) disease. There should be a low threshold for performing a renal biopsy unless there is a very obvious cause.

The patient with CKD stages 3–5

(See Section 5.)

These referrals are made for one of two reasons. First because an estimated GFR (eGFR) has been interpreted as a stage of CKD, for example, 'an eGFR of 45–59 mL/min/1.73m^2 indicates stage 3A kidney disease'. A decision as to whether individuals with a reduced eGFR need a formal nephrological assessment will depend on their

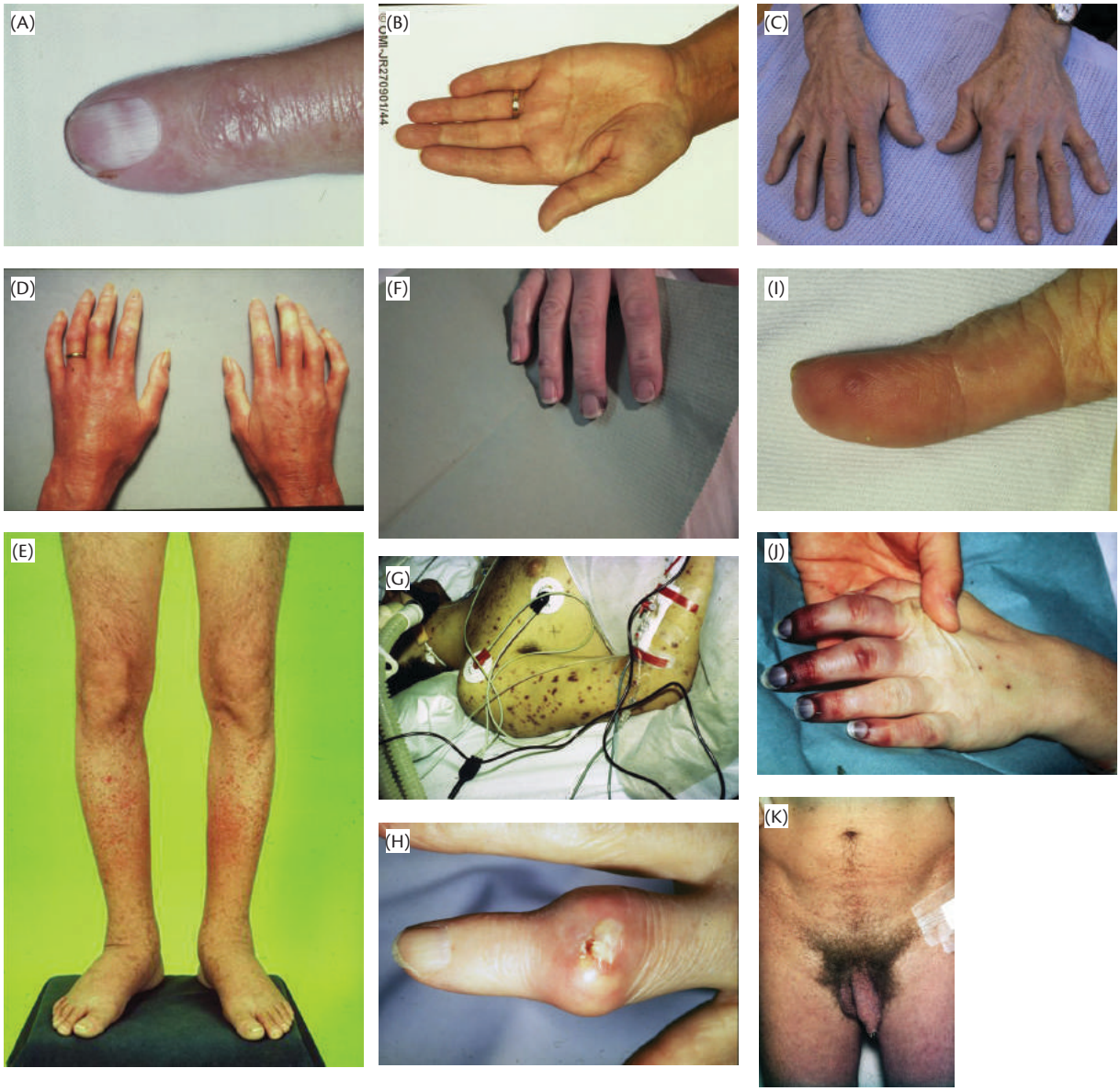

Fig. 5.1 Physical signs on general examination of the hands and peripheries. (A) White bands in the nails—evidence of hypoalbuminaemia in a patient who had an episode of nephrotic syndrome. (B) Palmar crease hyperpigmentation in a patient referred with hyperkalaemia caused by adrenal failure (Addison's disease). (C) Broad fingers in a potential living donor found to be hypertensive and acromegalic. (D) White shiny hands in a patient with scleroderma. (E) Limb purpura in a patient with the nephritic syndrome caused by type 2 essential cryoglobulinaemia. (F) A digital infarct in a patient with microscopic polyangiitis. (G) Widespread purpura in a young man with AKI and disseminated intravascular coagulation caused by meningococcal septicaemia. (H) Gouty tophus in a patient on long-term diuretics. (I) Finger pulp infarct in a patient with nephritic syndrome caused by endocarditis. (J) Digital ischaemia in a patient with AKI and disseminated intravascular coagulation following a dog bite. The infecting organism was *Capnocytophaga canimorsus*. (K) Angiokeratoma corporis diffusum I in the bathing trunk distribution in a patient with Anderson–Fabry disease.

underlying co-morbid conditions, age, and the rate of change. Is this actually acute kidney injury (AKI) in an early stage or CKD? The common trap is the older patient with non-specific symptoms and a lower than predicted GFR and a bland urine sediment attributed to 'CKD' who actually has AKI caused by interstitial nephritis or myeloma. These dilemmas are explored and recommendations made in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline (Lameire et al., 2013).

The second reason is that a patient has presented with symptoms, for example, of anaemia and routine testing has shown that renal function is more or less abnormal.

The first referral

The first task is to confirm that the patient does indeed have CKD. The eGFR may misrepresent the true renal function so one needs to take account of ethnicity, intercurrent events, the consumption of