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INCIDENCE OF INFECTIOUS DISEASES IN PATIENTS WITH RENAL DISEASES

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ABSTRACT
Infection is an invasion of an organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to the infectious agents and the toxins they produce. Patients with renal compromised states are more susceptible to infection than normal individuals. In the pre-dialysis era, about 45% of patients with the renal compromised state suffering from infection required hospitalization, while a total of about 78% of the enrolled subjects needed hospitalization. It was assumed that the debility caused by the uremic state increased the risk of infection, and the reversal of uremia would reduce the risk of infection. Infections are a major contributor to morbidity and mortality in end-stage renal disease (ESRD) patients. A better understanding of the interplay between infectious processes and ESRD may eventually lead to the development of targeted treatment strategies aimed at lowering overall disease morbidity and mortality. Monogenic causes are a major contributor to the development of adult chronic kidney disease (CKD). Recent studies identified a genetic cause in 10% to 20% of adults with CKD. With the introduction of whole-exome sequencing (WES) into clinical mainstay, this proportion is expected to increase in the future. Once patients develop CKD/ESRD due to a genetic cause, secondary changes, such as a compromised immune status, affect overall disease progression and clinical outcomes. Stratification according to genotype may enable us to study its effects on secondary disease outcomes, such as infectious risk. Moreover, this knowledge will enable us to better understand the molecular interplay between primary disease and secondary disease outcomes.The main aim of the study is to report the incidence of infectious diseases in patients with renal compromised state and appropriate measures to be considered to control infectious conditions.

Keywords: Incidence of infectious diseases, Renal compromised state, Renal disease.

Introduction
Chronic kidney disease (CKD) is a major public health concern and a major source of loss in expected remaining lifetime. In the US alone, 26 million individuals have CKD and millions of others are at risk.[1] The impact on life expectancy is particularly evident with kidney disease progression, with the worst outcome in patients with end-stage renal disease (ESRD). For a patient with a glomerular filtration rate (GFR) of 35 mL/min/1.73 m^2 (ie, CKD G3), the remaining life expectancy is reduced by a staggering 50%. However, for those patients who progress to ESRD, the current median life

expectancy at age 35 to 39 years is a mere 13.5 years.[2] This highlights the importance of elucidating the underlying causes contributing to morbidity and mortality in this particular cohort.

Infections are one of the main causes of mortality and morbidity in ESRD patients. They are among the leading causes of hospitalizations and are the third most common cause of mortality just after cardiovascular diseases and treatment withdrawal.[3] Notably, dialysis patients have a 30- to 50-fold higher risk of mortality secondary to sepsis compared with controls.[4] Therefore, a better understanding of how infection contributes to the increased risk in ESRD patients may eventually lead to the application of targeted strategies aimed at lowering morbidity and mortality.

In this review, we will present a transdisciplinary approach that aims to (1) illustrate how an altered immune status affects the clinical course of a primary kidney disease, by using autosomal dominant polycystic kidney disease (ADPKD), which is the most common monogenic cause of ESRD in adults, as an example; (2) describe how the immune system in ESRD patients functions differently compared with healthy individuals; and (3) discuss how recent technological advances in genomic medicine may provide us with the opportunity to fully unravel the underlying disease mechanisms and hopefully lead to the development of novel targeted treatment strategies (Figure 1).

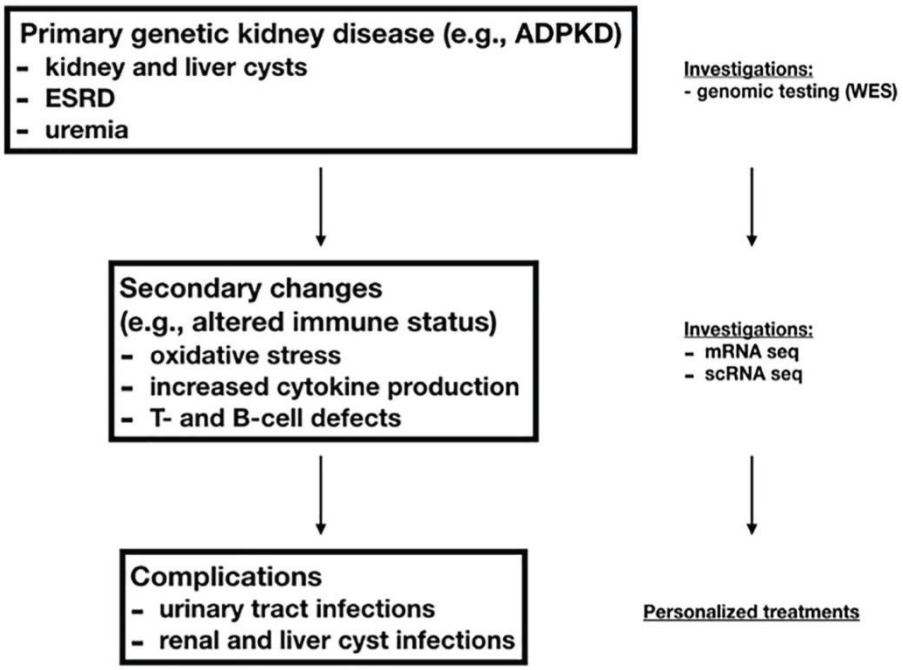

Figure 1. Infection in dialysis patients: a transdisciplinary perspective.

Note. While ADPKD is the most common monogenic cause of adult CKD, the implementation of WES into clinical practice has identified many other monogenic causes of adult CKD. Technologies such as scRNA-seq and dual RNA-seq applied to primary monogenic kidney diseases promise to provide direct insight into the molecular interplay of host and pathogen, which will hopefully lead to the development of novel targeted therapies for the treatment of infectious complications in patients with CKD and ESRD. ADPKD = autosomal dominant polycystic kidney disease; ESRD = end-stage renal disease; WES = whole-exome sequencing; mRNA-seq = messenger RNA sequencing; scRNA-seq = single-cell RNA sequencing; CKD = chronic kidney disease.

Viral Infections

A list of viral infections and associated nephropathies is shown in Table 1. Although any acute viral infection can lead to an immune-complex proliferative GN, however the following viral infections are common and induce kidney injuries by various mechanisms including direct cytopathic effects to immune complex mediated GN and vasculitis as well. Hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), human immunodeficiency virus (HIV), dengue virus, and Hantavirus infections can induce glomeruolpathy. Many of the virus infections like parvovirus, Epstein-Barr virus

(EBV), and cytomegalovirus (CMV) have been associated with very severe injury in the form of collapsing focal segmental glomerulosclerosis (FSGS).

TABLE 1. Viral infections and associated nephropathies.

Virus	Renal involvement
ACUTE	
Dengue	ATN, ICGN, MesPGN
Hantavirus HFRS	ATN, MesPGN
Varicella-zoster	DPGN
Parvovirus	ICGN, PAN, TMA, HSP
HAV	ICGN, MesPGN, ATN
HBV	ATN, DPGN
CMV	cFSGS, MN, IgA, HSP, ICGN, MPGN, TMA
EBV	ICGN, MN, MsPGN
SUBACUTE	
Parvovirus	cFSGS
EBV	cFSGS, MN
HBV	PAN
HCV	PAN
CHRONIC	
HBV	MN, Type I MPGN, MPGN1, MC, PAN, IgA, FSGS
HIV	HIVAN, HIVICK, ncFSGS, TMA
HCV	MPGN1, MC,MPGN2, PAN, IgA, MN

ICGN, immune-complex glomerulonephritis; MesPGN, mesangial proliferative GN; HFRS, hemorrhagic fever and renal syndrome; DPGN, diffuse proliferative GN; PAN, polyarteritis nodosa; PAN, polyarteritis nodosa; TMA, thrombotic microangiopathy; HAV, hepatitis A virus; HBV, hepatitis B virus; CMV, cytomegalovirus; cFSGS, collapsing FSGS; ncFSGS, non-collapsing FSGS; MN, membranous glomerulopathy; HSP, Henoch Shoenlein purpura; MPGN, membranoproliferative GN; EBV, Epstein-Barr virus; MC, mixed cryoglobulinemia; HIVAN, HIV-associated nephropathy; HIVICK, HIV immune complex disease of the kidney.

Hepatitis B Virus

Involvement of the kidney is an important extra-hepatic manifestation of HBV infection. With chronic HBV infection, renal disease is observed in up to 3–20% of patients (6). The histologic manifestations of HBV-associated renal disease can be classified as those that occur as a result of either immune-complex glomerulonephritis i.e., membranous glomerulonephritis (MGN), membranoproliferative GN (MPGN), cryoglobulinemic GN and IgA nephropathy (IgAN), or immune complex-related vasculitis i.e., polyarteritis nodosa (PAN) (7). MGN is more common in children whereas mesangioproliferative GN (MesPGN) and IgA deposits are common in adults. Kidney Disease Improving Global Outcomes (KDIGO) recommends the use of interferon or oral antiviral agents that consist of either one of nucleotides (adefovir dipivoxil, tenofovir disoproxil fumarate, tenofovir alafenamide) or nucleoside (lamivudine, entecavir, and telbivudine) reverse transcription inhibitors for treatment of HBV related GN and vasculitis (8). Corticosteroids may be given for a period of < 6 months without a significant effect on liver disease, HBV viremia, or patient morbidity or mortality as long as concomitant antiviral therapy is used (8). An algorithm of suggested approach has been shown in Figure 2 (9). Adefovir and Tenofovir are associated with nephrotoxicity, proximal tubular damage, fanconi syndrome, and osteomalacia. Entecavir is associated with lactic acidosis. Telbivudine is known to cause myopathy, increase creatine kinase, peripheral neuropathy, however may be renoprotective (10). Dose adjustment of drugs according to creatinine clearance should always be kept in mind. Universal vaccination has decreased childhood cases of HBV membranous nephropathy related to horizontal transmission of the virus. HBV infection in renal transplant recipient

should be treated with a NA and usually continued for as long as immunosuppressive therapy lasts or at least for 24 months (9, 10).

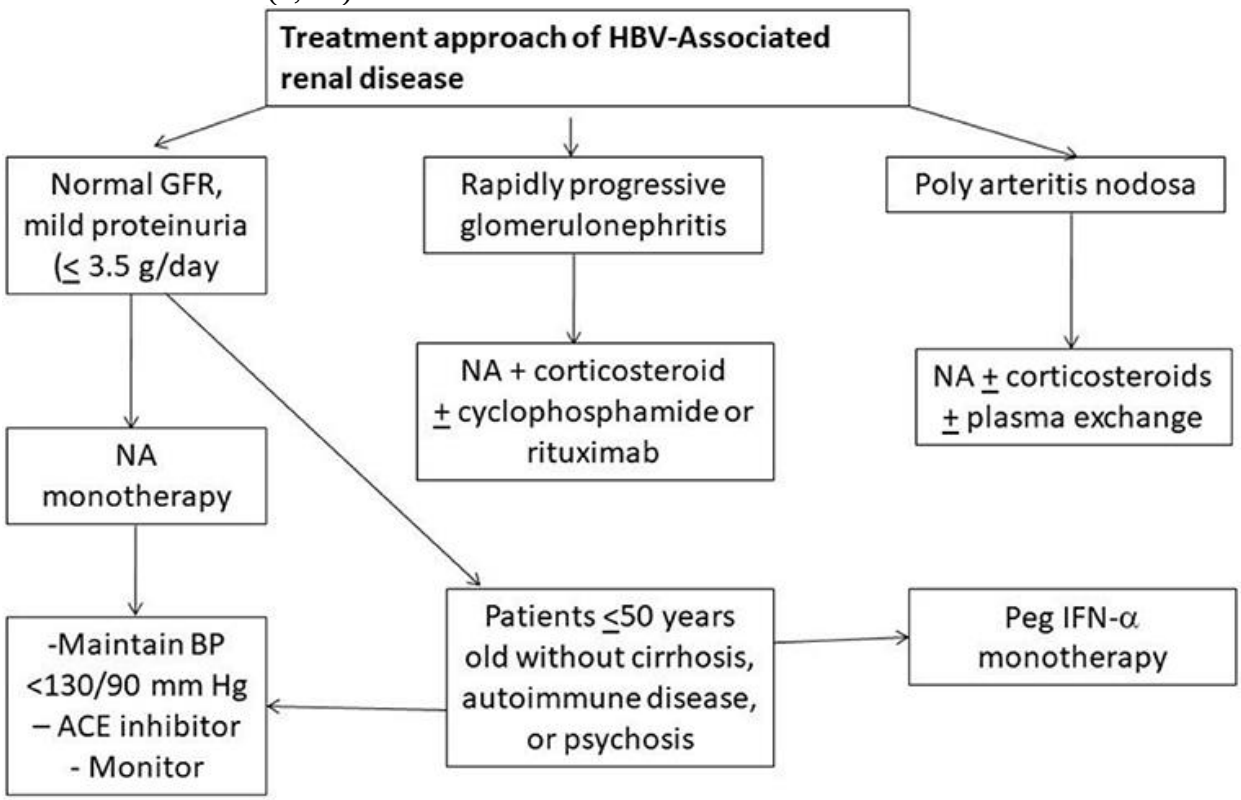

FIGURE 1. Algorithm showing treatment approach to hepatitis B associated renal diseases (NA, Nucleotide/Nucleoside antagonist); ACE, angiotensin converting enzyme).

Hepatitis C Virus

HCV-associated glomerular disease is primarily due to viral antigen-immune complex formation with their deposition on glomerular basement membrane. The pathologic hallmark is type 1 MPGN with or without type 2 mixed cryoglobulinemia. In addition, immune complex deposition in medium sized blood vessels may lead to PAN similar to HBV (11). Other lesions like MesPGN, focal proliferative GN, and IgAN have also been reported. It is important to note that renal dysfunction due to HCV rarely occurs because of GN (< 10%) and the majority manifest as a consequence of liver disease in form of acute tubular necrosis (ATN), hepatorenal syndrome, and pre-renal azotemia due to the use of diuretics (12). Interferon used to be the mainstream of therapy in the past, but the need for prolonged therapy, poor tolerance, an unsatisfactory sustained viral response and furthermore risk of rejection in renal transplant recipients limited its compliance and use (13). The recent development of potent direct acting anti-viral agents (DAAs) against HCV has enabled successful eradication of HCV with tolerable side effects. The use of DAAs resulted in disappearance of cryoglobulinemia, and resolution of glomerular lesions and are now drugs of first choice in HCV-related glomerular diseases (14). In aggressive disease like cryoglobulinemic vasculitis with impending organ failure, along with control of viremia, immunosuppressive agents (i.e., glucocorticoids, cyclophosphamide, and plasmapheresis) may be warranted to salvage the kidney (15). Wider availability of low cost and generic DDAs in many developing countries is intercepting HCV infections in patients on dialysis and transplantation (16, 17). Recently, KDIGO 2018 guideline (18) emphasized monitoring with nucleic acid amplification test (NAT) in case of HCV infection and also laid down algorithm for the use of DAAs for different specific genotypes and approach for a HCV infected patient for renal transplant with availability of DDAs (Figure 3).

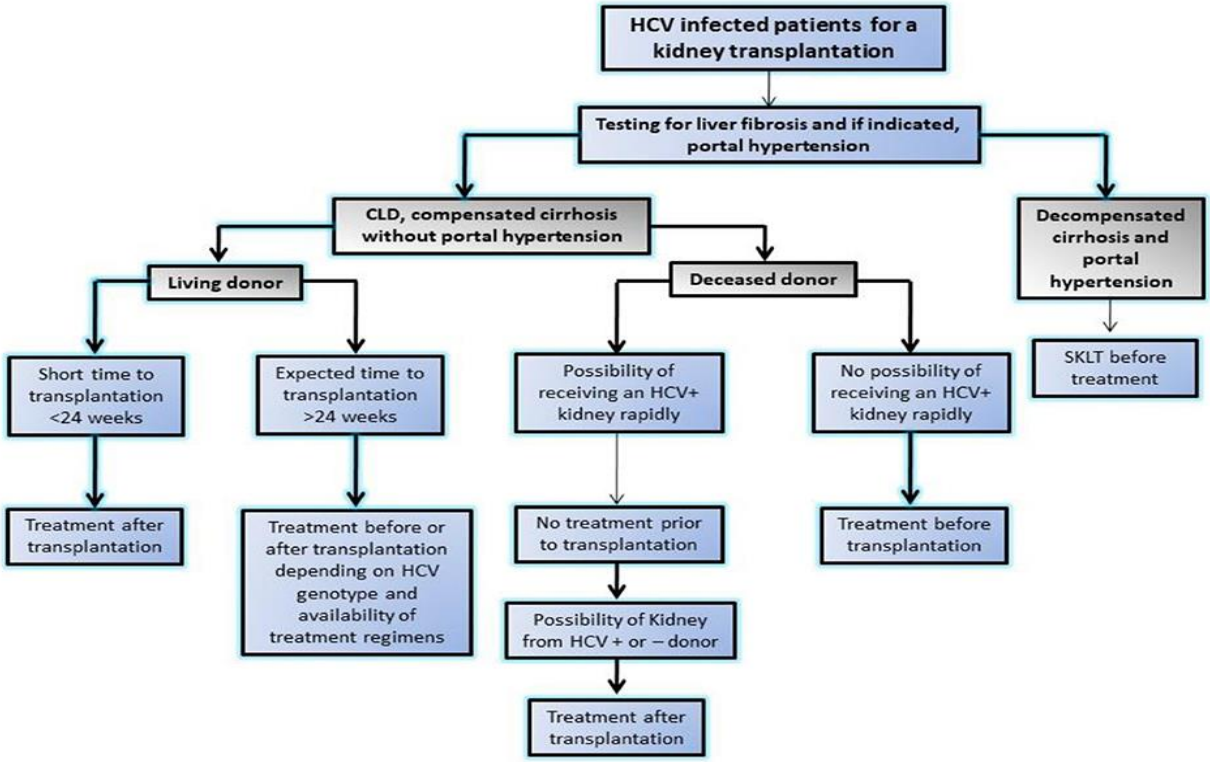

FIGURE 3. Algorithm showing approach to HCV infected patients for kidney transplantation in modern era of highly effective directly acting anti-viral agents by Kidney disease initiative and global outcome (KDIGO). SKLT, simultaneous liver kidney transplantation.

Human Immunodeficiency Virus

Renal diseases in HIV infection manifest in many ways varying from direct invasion by HIV, formation of immune complexes, related to drugs used for treatment, dehydration and various other bacterial, and viral co-infections (21). The demographics of HIV-associated renal disease depend on the population being reported. In the United States and Europe where highly active antiretroviral therapy (HAART) is prevalent, non-collapsing focal segmental glomerulosclerosis (FSGS) is the most common glomerular lesion (19). HIV-associated nephropathy (HIVAN) occurs due to direct viral infection of visceral and parietal epithelial cells characterized by a combination of collapsing FSGS, tubular microcystic dilation, interstitial nephritis, and the presence of intra-cytoplasmic tubuloreticular inclusions without the presence of immune complexes (22). Most patients are HAART naive and of black race with apolipoprotein-1 (APOL1) G1 /G2 variants with various degree of proteinuria and renal dysfunction (23). Median renal survival in patients with zero or one risk allele is lower than two APOL1 risk allele (23). HARRT is effective in reversing renal dysfunction and induce histological regression. Progressive decline in renal function in a patient treated for HIVAN with HAART may be due to various causes i.e., drug toxicity, immune reconstitution syndrome in form of acute interstitial nephritis, immune-complex GN or co-infection with HBV or HCV (24, 25). HIV immune complex disease of the kidney (HIVICK) results from deposition of immune complexes consisting of either HIV antigens or post-infectious immune complexes following other co-infections (23). It represents a pathophysiologic grouping of a wide variety of glomerular diseases i.e., post-infectious GN, membranous GN, IgA nephropathy, MPGN and a “lupus-like” diffuse proliferative GN each with different presentation and prognosis (24). HAART has been effective in some but not all. This may be due to heterogeneous nature of HIVICK and permanent injury to the glomerular basement membrane by immune deposits (26). At present, HAART remains the cornerstone of the therapy in HIV induced kidney diseases. HIV vaccination in future may be step forward in prevention of such diseases.

Dengue Virus

Dengue is a worldwide infection with 40% of the global population living in endemic areas especially Southeast Asia, and Pacific Islands. Infections occur through the bite of the female Aedes aegyptii. Dengue is classified into specific syndromes: dengue fever, dengue hemorrhagic fever, and dengue shock syndrome (27). AKI occurs in ~10–33% of patients and is primarily associated with dengue hemorrhagic fever and dengue shock syndrome. AKI results from ATN as a consequence of hypovolemia and capillary leak and/or rhabdomyolysis (28). Glomerulonephritis in dengue is also well-described which may result from immune-complex deposition or, because of direct viral entry into renal tissue (29). Predominant mesangial hypercellularity with immune complexes and IgM deposition or diffuse proliferative pattern is usually the histological picture. The presence of hematuria and proteinuria (both sub-nephrotic and nephrotic) helps distinguish these cases from typical ATN. Treatment strategies remain limited to supportive management in all categories of dengue. Dengue infection in renal transplant recipients may be relatively asymptomatic under effect of immunosuppression; however infection in early period may lead to death (30).

Hantavirus

Hantaviruses are RNA viruses that belong to the Bunyaviridae family with wild rodent as reservoir. Renal involvement may occur up to 30–40% of cases. Two syndromes can develop: hemorrhagic fever with renal syndrome (HFRS), also called nephropathica epidemica; and Hantavirus pulmonary syndrome (HPS) (31). HFRS manifests clinically with sudden onset of flu like syndrome with fever, myalgia, and headache followed by gastrointestinal symptoms and AKI with oliguria. HFRS leads to renal edema and retroperitoneal leakage of fluid. Acute tubulointerstitial nephritis with mononuclear cells and CD8+cell infiltration is the most prominent finding in the renal histopathology (32). HFRS occurs primarily in Europe and Asia (Old World Hanta) and is caused by the four major Old World Hantavirus serotypes: Hantaan, Dobrava-Belgrade, Puumala, and Seoul viruses. The disease severity and case fatality rate of HFRS varies with the serotype i.e., 0.3% for Puumala infections, 1% for Seoul, 5–10% for Hantaan, and up to 15% for Dobrava. HPS is observed in North-America, Mexico and Panama (New World Hanta) with very high mortality rate up to 30–40% within 24–48 h of admission (32, 33). Hantavirus and other rodent borne disease like leptospirosis have been implicated as one of the potential explanation for Mesoamerican nephropathy (34). No specific therapy is available for Hantavirus infection, management remains conservative and preventive strategies with vaccination are limited as an approved vaccine for Hantavirus infection is still underway.

Parvovirus

Parvovirus may be associated with three different clinical settings in nephrology practices i.e., glomerulopathy, anemia in ESRD patients and pure red cell aplasia post renal transplantation (35). However, association between parvovirus and glomerular injury is still circumstantial. Viral-induced FSGS has been associated with parvovirus B19. Parvovirus DNA has been identified in renal endothelial and epithelial cells, both visceral and parietal cells, causing collapsing FSGS (90%), idiopathic FSGS (80%), MGN (50%), and minimal change disease (50%) (36). Effective antiviral is lacking, however, Intravenous immunoglobulin may be required in case of red cell aplasia and bone marrow suppression.

Polyoma Virus

Polyoma virus is ubiquitous virus, with seroprevalence of 70–90% in adults, showing reactivation intermittently in both immunocompetent and immunosuppressant individuals (37, 38). Polyoma virus-associated nephropathy (PVAN) is an important infection in patients with renal allograft recipients, affecting 3–10% of patients, causing graft loss in about half of the cases (38). The BK virus exhibits tropism for the renal tubular cells. Immunosupression leads to reactivation of the latent infection and causes graft dysfunction. Viral replication leads characteristic epithelial cell enlargement, karyomegaly, and nuclear inclusion bodies, often associated with an interstitial inflammatory response. Diagnosis is confirmed by immunohistochemistry using an antibody to SV40

large T antigen, and/or electron microscopy showing virions of 40 nm diameter. Monitoring using nucleic acid testing of BKV in blood and urine is recommended for early detection of infection. As there is no specific therapy, mainstay of management of PVAN is reduction of the immunosuppressive therapy and possibly use of various adjuvant medications e.g., cidofovir, leflunomide, and fluoroquinolones (39).

Personalized Medicine to Improve Patient Outcomes in CKD and ESRD

Over the past 100 years, clinical medicine experienced substantial success with the advent of population-based treatment and screening approaches; however, it has become increasingly clear that to further improve patients' outcomes, human biology demands an ever more personalized treatment approach. One of the major impediments to a truly "personalized" approach is our current lack of insight into the exact details of many of the underlying disease mechanisms. The introduction of whole-exome sequencing (WES) into clinical practice, which enables us to simultaneously analyze all protein-coding genes in the genome, has offered some promise to get one step closer toward this ambitious goal.

WES techniques consist of 2 main steps. First, regions of the DNA encoding proteins are captured and enriched. These regions are called exons and, together with introns, make up the roughly 20 000 genes that constitute around 1% of the human genome. Subsequently, the exonic DNA is sequenced by using high-throughput DNA sequencing technology. The parallel analysis of thousands of genes drastically increases the likelihood to identify the underlying cause in diseases where there is more than one possible genetic etiology.74 The increasing clinical implementation of WES shattered the paradigm that genetic diseases are primarily identified in pediatric nephrology populations.

ADPKD is the commonest monogenic cause of adult-onset hereditary kidney disease. However, recently, it has been demonstrated that many more genes contribute to the development of adult CKD. For example, Lata et al identified diagnostic mutations in 22 of 92 adult CKD patients (24%), encompassing 13 distinct genetic disorders.75 Importantly, the authors report that diagnosis affected clinical management in most identified cases, including initiation of targeted surveillance, familial screening to guide donor selection for transplantation, and changes in therapy. Similarly, Sadowski et al identified a single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome.76 The largest and most recent study to date demonstrated that exome sequencing in a combined cohort of more than 3000 patients with CKD yielded a diagnosis in 10% of patients.77 Steroid-resistant nephrotic syndrome is the second most frequent cause of ESRD in the first 2 decades of life and is characterized by genetic heterogeneity with many different genes involved in disease development. Interestingly, patients presenting between 19 and 25 years of life were found to have a causative genetic variant in 21%. This finding has been corroborated and extended by Sen et al, who demonstrated in 302 patients, who either presented with nephrotic syndrome (n = 267) or a suspicion of Alport syndrome (n = 35), that next-generation sequencing gene panel testing determined a likely genetic cause of disease in 20% of pediatric, 21.3% of adult nephrotic cases, and 48.6% of hematuria/Alport syndrome patients.78

It is foreseeable that the diagnostic utility of genomic approaches such as WES will be improved with our increasing understanding of disease mechanisms and the identification of novel disease genes.

Our ability to identify the causative genes of primary kidney disease offers the unique opportunity to fully unravel the underlying molecular pathomechanisms and develop novel targeted therapies. However, once the primary disease (eg, ADPKD) progresses and chronic renal failure advances toward ESRD, secondary alterations ensue and permanently alter the function of other organ systems, such as immununosuppression with increased infectious disease risk. These changes compound with the primary defect, setting in motion a detrimental spiral of disease progression. Despite its diagnostic usefulness, WES is of little help in improving our understanding of these secondary changes. This can be explained by the fact that these secondary changes are not due to an alteration of primary genetic information (ie, a pathogenic variant in the PKD1 or PKD2 gene) but are rather due to secondary changes in gene expression profiles and ensuing molecular changes. The upregulated genes of specific pathways constitute a differential gene expression profile with an altered metabolite level. Notably,

these secondary disease mechanisms may vary depending on the underlying nature of the primary genetic defect. While the infectious disease risk is well documented in ADPKD, there is currently insufficient data on the infectious risk in other monogenic causes of ESRD. Studies using genotype for risk stratification may enable us to shed light on this.

What does the future hold? The transcriptomePrevious studies demonstrated that individuals vary genetically in their response to infectious challenges; however, until recently it has been difficult to functionally study the gene-environment interplay.79 Moreover, as mentioned above, it has long been known that chronic uremia increases the risk for infection. This is highlighted by a study by Zawada et al, who demonstrated genome-wide epigenetic alterations in patients with CKD, identifying over 100 candidate genes associated with proatherogenic and inflammatory processes.80 Epigenetics is the study of heritable changes in gene expression; however, the most direct way of studying epigenetic alterations is by studying its effects on gene expression (ie, the transcriptome). The recent application of novel technologies, such as RNA sequencing (RNA-seq) and single-cell RNA sequencing (scRNA-seq), allows one to assess differential gene expression in a temporospatial manner. While RNA-seq analyzes the transcriptome (ie, the set of all RNA molecules) in a cell population, scRNA-seq analyzes the transcriptome specific to a singular cell type. For example, Chu et al employed RNA-seq of serial kidney biopsies in dogs with X-linked hereditary nephropathy and identified 70 differentially expressed genes. The group revealed upregulation of inflammatory pathways, such as integrin signaling, T-cell activation, and chemokine and cytokine signaling.81 RNA-seq has also been used in the setting of ADPKD. In a combined meta-analysis of PKD expression profiles in Pkd1-mutant mouse models, it has been shown that 1515 genes are commonly dysregulated. Malas et al demonstrate that this PKD signature was significantly enriched for genes directly involved in kidney injury repair.82 Notably, nuclear factor-kappa B signaling, epithelial-mesenchymal transition, inflammatory response, hypoxia, and metabolism were among the most prominent repair-related biological processes. While these studies highlight the usefulness of RNA-seq to study changes in gene expression throughout the entire organ, more recent studies have shown that this technique can be used to study gene expression at the single-cell level. Several groups have demonstrated that scRNA-seq allows reliable distinction of different kidney cell types in mice and humans, which in turn allows the study of cell-type specific gene expression levels.83,84 In a recent review, Malone et al discuss how the use of scRNA-seq, which has been established in the fields of neuroscience, stem cells, and cancer, can be extended to the field of nephrology.85 In particular, they describe a study by Der et al, who uses this method in patients with lupus nephritis to correlate clinical parameters and treatment response with interferon to the gene expression levels of interferon responsive genes in tubular cells obtained through kidney biopsy.86 One particularly intriguing aspect of using this novel technique of high-resolution RNA sequencing down to the single-cell level is that it allows for the parallel analysis of different organisms interacting with each other; for example, during infectious processes, Westermann et al employed so called “dual RNA-seq” studies to simultaneously capture all classes of coding and noncoding transcripts in both the pathogen and the host, providing direct insight into the host-pathogen molecular interplay.87 Applying this technology to a population, such as patients with ESRD in ADPKD and other monogenic causes of CKD, may enable us to elucidate why some patients are particularly susceptible to certain types of infections.

Translational research: The value of a transdisciplinary, patient-centered approachThere has been increasing criticism regarding the lack of translation of fundamental research findings into effective public health interventions. Current strategies are hampered by an increasing amount of seemingly unrelated findings, exceedingly high costs, long timelines, and, unfortunately, poor performance in clinical trials.88 This lack of “translationality” may be partly explained by the complex nature of many of the currently most important health problems such as chronic renal disease, which is highly diverse, both etiologically and phenotypically. Current efforts aimed at increasing effectiveness emphasize the potential usefulness of transdisciplinary approaches to complex health problems, and their potential to overcome interdisciplinary and institutional boundaries by creating collaborative efforts.88

The health care sector has lagged behind other sectors in moving toward consumer/patient-centred practices. The Can-SOLVE CKD Network has demonstrated successfully how to overcome some of these challenges by creating the opportunity for researchers across Canada to take part in patient-centred research projects, thereby incorporating patients' perspectives early on when identifying key research questions. As part of this effort, a current multicenter randomized trial aims to improve the timing of dialysis initiation in patients with CKD, and a study from Ontario identified the main barriers to living donor kidney transplantation by studying the perspective of living kidney donors and recipients.89,90 For ADPKD, a group from the United Kingdom has shown how a patient-centred approach may help to improve pain management in this cohort.91

There is currently very limited evidence on how the implementation of genomic tests into clinical practice may affect patient-centred outcomes. However, one of the main reasons for this lack of information is the fact that many studies do not include outcomes that matter most to patients.92 Hence, it has been recommended that research team leaders use real-world settings and seek advice from patients about which outcomes matter most.92,93

Findings of Epidemiology of kidney disease

The prevalence of the various types and stages of kidney disease has grown considerably in recent years and will continue to do so. Factoring in the ageing population and excess deaths in high-risk populations during the Covid-19 pandemic, an estimated 7.19 million people in the UK have chronic kidney disease in 2023, more than 10% of the UK population. By 2033, this will increase to 7.61 million people. While the overall prevalence as a proportion of the age 16+ population is expected to remain constant, among the people with chronic kidney disease, the proportion of patients with later-stage chronic kidney disease is expected to increase from 45% to 51%

Rates of acute kidney injury will also continue to grow, although more slowly than chronic kidney disease. Based on historic trends, the incidence of acute kidney injury will increase from an estimated 615,000 episodes in 2022 to 637,000 by 2033. For dialysis and transplantation, a broad range of potential future demand was calculated. The constrained view assumes NHS capacity continues to grow at current rates based on the actual numbers of patients treated over the past 10 years, while the unconstrained view estimates the number of people who may need dialysis based on how quickly people progress through the stages of kidney disease. In the unconstrained view of demand, which factors in all potential unmet need, the number of patients requiring dialysis could rise to 143,000, while the demand for transplantation could be as high as 12,000 per year by 2033.

Modelling of interventions to manage the burden of chronic kidney disease

There is a growing body of evidence indicating that the burden of chronic kidney disease can be reduced through early detection, pharmacological intervention and outreach. A key objective for this report was to assess whether a basket of potential population-level interventions for managing chronic kidney disease, including end-stage kidney disease, could be cost-saving or cost-effective. Through the stakeholder engagement process, several interventions were cited as having the potential to improve clinical outcomes associated with chronic kidney disease. The following interventions were applied to the model: • Intervention 1. Early/improved diagnosis: This intervention targets underserved populations through outreach programmes to improve screening opportunities and increase early diagnosis and is illustrative of the benefits which can be achieved through well-targeted early/improved diagnosis in general. • Intervention 2. Improved CKD management: This intervention targets eligible patients with chronic kidney disease who are either untreated or not receiving standard care according to clinical guidelines (e.g. adequate blood pressure management). • Intervention 3. Use of SGLT-2 inhibitors: This intervention aims to increase uptake of new medications such as sodium-glucose transport protein 2 (SGLT-2) inhibitors to reduce cardiovascular events and slow progression to end-stage kidney disease. • Intervention 4. Increased rates of transplantation: This intervention models the impact of increased outreach and awareness to increase pre-emptive live donor transplants. It is illustrative of the benefits of improving transplantation rates more generally. The combined impact of these interventions was to prevent more than 10,000 deaths over the 10-year time horizon,

with 49,574 quality-adjusted life years saved (Table E2). This is predicted to cost £7,688 per quality-adjusted life years – significantly below the National Institute for Health and Care Excellence willingness-to-pay threshold of £20,000-£30,000 per quality-adjusted life year (QALY), meaning these interventions would be deemed cost effective. The modelling also predicts that the reduction in indirect costs (travel and lost economic productivity) of £445.7 million would more than offset the total increase in NHS costs of £381.1 million. All of the interventions individually or combined show a cost-effective or cost-saving Incremental Cost-Effectiveness Ratio (ICER).

Conclusion

Chronic kidney disease affects 13% of the global population and is predicted to be the fifth leading cause of premature death* by 2040. Premature death can be measured by life years lost, which takes into account frequency of death and age at which it occurs. It is calculated by multiplying the number of deaths by a global standard life expectancy at which death occurs. In the india, approximately 3.25 million adults are living with chronic kidney disease stages 3-5, and a total of 7.2 million adults have chronic kidney disease (all stages), more than 10% of the entire population. 3. By 2033, the number of people living with all-stage chronic kidney disease is projected to reach 7.6 million. This is mainly driven by an ageing population as well as risk factors such as diabetes, hypertension and cardiovascular disease, as well as other important factors such as health and economic inequalities. 4. Amongst those with chronic kidney disease, the proportion with later-stage chronic kidney disease (3-5) is expected to increase from 45% (3.25 million) to 51% (3.9 million). 5. Around 615,000 episodes of acute kidney injury occur each year, mainly among those who are already unwell or hospitalized for another reason. By 2033, the number of acute kidney injury episodes is projected to rise by 4% to 637,000.

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