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## INCIDENCE OF INFECTIOUS DISEASES IN PATIENTS SUFFERING FROM RENAL DISEASES

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### ABSTRACT

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.

#### Sources of information:

We conducted a literature review using search engines such as PubMed, PubMed central, and Medline, as well as cumulative knowledge from our respective areas of expertise.

#### Methods:

This is a transdisciplinary perspective on infectious complications in ESRD due to monogenic causes, such as autosomal dominant polycystic kidney disease (ADPKD), combining expertise in genomics and immunology.

#### Key findings:

In ADPKD, infection is a frequent complication manifesting primarily as lower urinary tract infection and less frequently as renal infection. Infectious episodes may be a direct consequence of a specific

underlying structural abnormality, for example the characteristic cysts, among others. However, evidence suggests that infectious disease risk is also increased in ESRD due to secondary not-well-understood disease mechanisms. These disease mechanisms may vary depending on the underlying nature of the primary disease. While the infectious disease risk is well documented in ADPKD, there are currently insufficient data on the risk in other monogenic causes of ESRD. WES in combination with novel technologies, such as RNA sequencing and single-cell RNA sequencing, can provide insight into the molecular mechanisms of disease progression in different monogenic causes of CKD/ESRD and may lead to the development of novel risk-stratification profiles in the future.

**Limitations:**

This is not a systematic review of the literature and the proposed perspective is tainted by the authors' point of view on the topic.

**Implications:**

WES in combination with novel technologies such as RNA sequencing may enable us to fully unravel underlying disease mechanisms and secondary disease outcomes in monogenic causes of CKD and better characterize individual risk profiles. This understanding will hopefully facilitate the development of novel targeted therapies.

**Keywords:** End-Stage Renal Disease, infection, immune system, polycystic kidney disease, monogenic kidney disease, whole-exome sequencing, RNA sequencing

**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<sup>2</sup> (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**).

*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.

### **The Impact of Primary Diseases: An Example**

In addition to the well-documented inflammatory uremic environment present in ESRD [5-7], infectious risk may be modulated by the patients' primary disease. In some cases, patients may be intrinsically immunosuppressed as a result of an autoimmune condition (eg, lupus) or may receive immunosuppressive drugs. Other disorders still may induce an increase in infectious episodes on the basis of specific structural abnormalities (**Table 1**).

ADPKD is the commonest inherited disorder of the kidneys, caused by mutations in the genes *PKD1* (OMIM 173900) and *PKD2* (OMIM 613095) [8]. It has a prevalence of 1:400 to 1:1000 and results in ESRD in men and women at a rate of 8.7 and 6.9 million per year, respectively, in the United States [9, 10].

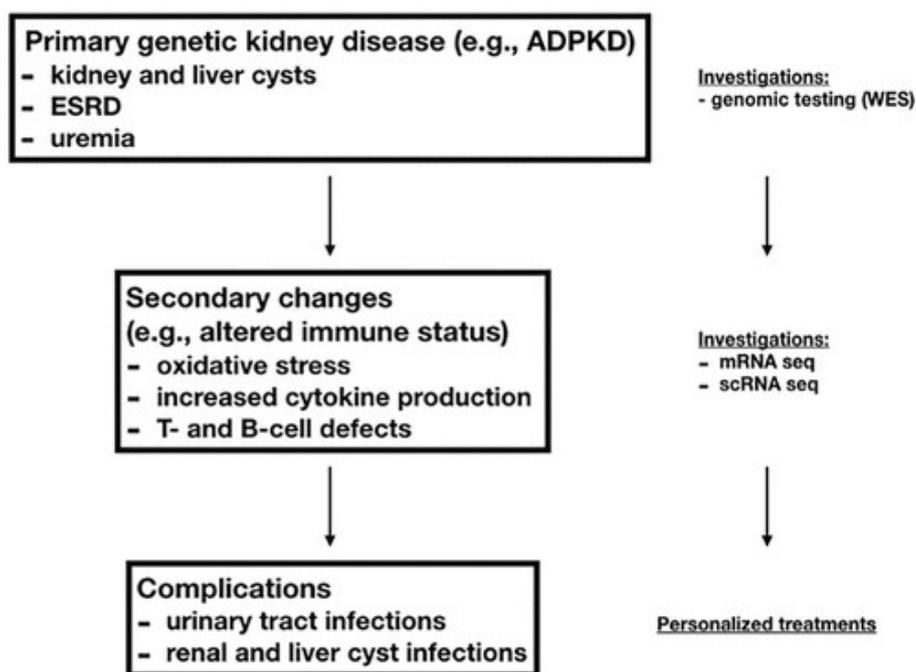


Figure 1: Infection in dialysis patients: a transdisciplinary perspective

Table 1: Infectious Risk Attributable to the Cause of Chronic Kidney Disease.

Etiology of chronic kidney disease	Risk attributable to the disease
Diabetes	Immunosuppression related to diabetes Accelerated vascular disease Diabetic foot
Autoimmune diseases	Use of immunosuppressive drugs to treat the disease
Systemic infection	Infectious risk if the infection is not cleared
Drugs	Chemotherapy and immunosuppressive drugs
Neoplasia (including amyloidosis)	Chemotherapy Primary disease (mostly hematopoietic malignancies)
Tubulointerstitial diseases such as urinary tract infections, stones, and obstruction	Recurrence of urinary tract infection (mostly if it was the primary disease, with struvites and with obstruction)
Vascular diseases (atherosclerosis, hypertension, ischemia, cholesterol emboli, thrombotic microangiopathy, systemic sclerosis)	Link between obesity and increase in morbidity in obese septic patients Poor blood flow and poor wound healing
Cystic and congenital diseases	Urinary tract infection with cystic diseases or structural damage
Structural	Urinary tract infection associated with reflux or obstruction.

As a major cause of ESRD, ADPKD represents an interesting model to study infection in advanced CKD. One possible limitation of this model is that in non-ESRD patients the increase in infectious risk is not due to an intrinsic deficiency of the immune system. Advantages include the rate of infectious episodes, the data available on infections in dialysis patients, and the variety of organ systems that can be affected.

Up to 19% of men and 68% of women report a history of lower urinary tract infection in ADPKD, which is a lot more than the 0.7% prevalence in the general population [11]. Renal infection due to ascending contamination (either pyelonephritis or cyst infection) is less frequent and it may lead to complications such as perinephric abscess, bacteremia, and death. Renal infection has been reported in up to 26% of hemodialysis

(HD) patients with ADPKD [12]. Predisposing factors for renal infection in ADPKD may include age, female gender, and invasive interventions on the urinary tract [13]. As with pyelonephritis, renal cyst infection should be suspected in the setting of acute abdominal pain with fever [14]. Liver cyst infection may resemble renal cyst infection clinically and therefore complicate diagnosis; however, a thorough radiological evaluation may point out the culprit cyst (eg, presence of intracystic gas) [15]. Other infectious syndromes include cholangitis, diverticulitis, and mitral valve disease complicated by endocarditis [5].

Cyst infection may occur at any stage of ADPKD, including in dialysis: in this subgroup, it appears to be more prevalent in patients with a history of cyst infection prior to the onset of dialysis [5]. In a case-control study comprising 50 ADPKD patients on renal replacement therapy, the prevalence and number of episodes of renal infection were more elevated in the ADPKD group compared with the control group consisting of non-ADPKD patients matched for sex, age, and approximate start of HD [16]. Moreover, liver cyst infections are more frequent in ADPKD patients once they are on HD [17].

Cyst infections are mainly caused by gram-negative bacilli from the enteric flora (eg, *Escherichia coli*) [15]. Lipid-soluble

antibiotics have shown good penetration into the cysts and should be favored over water-soluble antibiotics (cysts are structurally independent of the original tubule, and antibiotics have to cross the cyst wall to reach them) [5]. Therefore, fluoroquinolones and trimethoprim-sulfamethoxazole, which are lipid-soluble and have broad activity against gram-negative rods, are the two main antimicrobial classes used [15]. Interestingly, gram-positive bacteria were found to be almost as frequent in dialysis patients with hepatic cyst infection and positive cyst culture, with low susceptibility to levofloxacin, suggesting an alternative to fluoroquinolones as empirical treatment should sometimes be sought [15].

Cyst infection can be treated by a number of approaches. A systematic review analyzing renal cyst infection management showed that the first approach was antimicrobial therapy in 79% of cases and was associated with a high rate of failure (75%), requiring subsequent percutaneous intervention (27%) or surgery (37%) [14]. The authors set out to identify factors influencing antimicrobial treatment efficacy. CKD G3-5 was particularly frequent in patients failing initial treatment, possibly due to renal hypoperfusion leading to insufficient drug concentrations in vasculature and urine. Other associations with treatment failure were shorter duration

of treatment, large cysts (>5 cm), and postrenal obstruction. Therefore, cyst infection should be treated for a minimum of 6 weeks, large cysts should be decompressed, and stones should be removed as needed [5, 12]. Also, in the setting of poor antibiotic penetration into the cyst and uremia-induced immunosuppression, case reports of intracystic antibiotic therapy showed some clinical benefits [18].

In summary, patients with APDKD suffer from numerous infectious complications, the main one being urinary tract infection. Infection rate is higher in ESRD. Targeted therapies exist but prove less efficient in complicated cases involving rare pathogens. There is a need to reinforce the anti-infective therapeutic arsenal in this population of patients.

### How Is the Immune System of End-Stage Renal Disease Patients Different?

ESRD patients can be considered immunocompromised as they have an increased risk of infection, a reduced response to vaccines [19-21], and are at high risk of immunodeficiency-related cancers [22]. As renal function decreases, there is a measurable increase in uremic toxins and cytokines leading to substantial oxidative stress and release of inflammatory cytokines. This inflammatory uremic milieu has been associated with disturbance in both innate [6] and adaptive immunity (Figure 2) [7]. In addition, dialysis per se can cause inflammation and contribute to the altered immune system [23]. However, the specific contribution of each dialysis modality on individual components of the immune system has not been thoroughly studied.

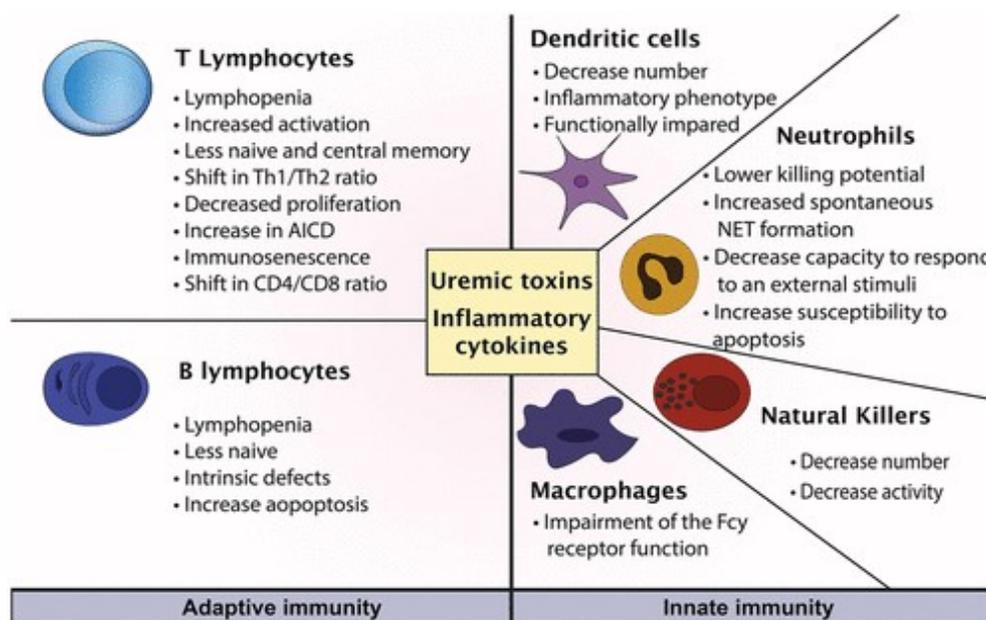


Figure 2: Impact of uremia on the immune system

Note. This figure summarizes the changes in the innate and adaptive immune system in end-stage renal disease patients. AICD = activation-induced cell death

### ***Alterations to the innate immunity caused by ESRD***

Neutrophils play an important role in the acute phase of inflammation, particularly against bacterial and fungal infections. Neutrophils of CKD patients, as well as patients with diabetes, hypertension, and cigarette smokers, seem to be chronically “primed,” as opposed to quiescent, and have an increased spontaneous neutrophil extracellular traps (NET) formation. As such, they can contribute to the chronic systemic oxidative stress inflammatory processes and increase cardiovascular risk [24-26]. However, neutrophils from patients on maintenance HD are not as good to act “on-demand” and are less effective to respond to an external stimuli, such as bacterial infection [27-28] and more susceptible to apoptosis after being activated.<sup>29</sup> The causal relationship between the uremic milieu and neutrophil impairment is reflected by the slight improvement of the killing potential by dialysis [29]. However, restoration of a normal activity is only achieved by transplantation [30].

Natural killer (NK) cells play an important role in the defense against infection and tumor. Patients on chronic intermittent HD have a decreased number of CD3<sup>-</sup>CD16<sup>+</sup>CD56<sup>+</sup> NK cells [31]. Their NK cells are also less reactive [32], because

of alterations in their activation markers [31, 33] and chemokine receptors [31].

Dendritic cells (DC) are potent antigen-presenting cells and are key messengers between the innate and the adaptive immune system. They are protective against pathogens, tumors, and self-tolerance. Both myeloid (mDC) and plasmacytoid (pDC) DCs are deficient in ESRD patients [34-36]. Uremia is also associated with an increase in a more inflammatory type of monocytes (CD14<sup>+</sup>CD16<sup>+</sup>) leading to an increase propensity to generate immature and mature mDCs in vitro [37, 38]. However, those DCs are functionally impaired [39, 41]. As for pDCs, exposition to uremic toxins also inhibits some of their function in vitro, such as interferon-alpha production [36, 42]. Finally, both mDC and pDC function can be restored by transplantation [43].

Macrophages are useful against bacteria by recognition of antibody-coated pathogens with their Fcγ receptor followed by phagocytosis. However, there is an impairment of the Fcγ receptor function in ESRD patients on HD [44].

### ***Alterations to the adaptive immunity caused by ESRD***

Although the decline in renal function has been associated with abnormalities in almost all of the immune cell subtypes, immunodeficiency-related morbidity and

mortality of ESRD patients have been largely attributed to defects in T lymphocytes. Notably, uremia is associated with a decrease in T cell number [45], an increase in their activation [45], " changes in their compartment composition such as a loss of naive and central memory cells, a shift in the Th1/Th2ratio [45, 47], and decreased proliferation in response to external stimuli [46-48].

Lymphopenia present in ESRD patients could be explained by a lower T cell homeostatic proliferation that may be caused by a decrease in Interleukin 7, an increase in apoptosis [45, 47], or a combination of both. Indeed, T cell activation-induced apoptosis is higher in HD patients compared with uremic nondialyzed patients, and both are higher compared with healthy controls.

Uremia is also associated with premature aging (immunosenescence) of T lymphocytes, which is not improved by transplantation. Indeed, T cells from ESRD patients are comparable with T cells from individuals 20 to 30 years older. This immunological aging is characterized by a premature decline in thymic function, a decrease in relative telomere length, more differentiated T-cells (less naive ones and more memory T cells with terminal differentiation) and a shift in CD4/CD8 ratio. In addition, immunodeficiency associated with uremia could promote

CMV reactivation which is associated with the generation of a proinflammatory helper T cell type, CD4<sup>+</sup>CD28<sup>-</sup> which has been independently associated with an increase in cardiovascular disease.

B cells are also affected by uremia, and ESRD patients tend to have B cell lymphocytopenia, intrinsic B cell function defects, suboptimal T helper cell function, increase in B cell apoptosis, and abnormal distribution of B cell subsets, such as fewer memory B cells. Finally, invariant NK T cells are reduced in ESRD.

A clinically relevant example of the consequences of an altered adaptive immune system is the decrease in hepatitis B vaccine response observed in patients with ESRD [19-21]. Indeed, in a population of CKD patients, GFR was an independent predictive factor of seroconversion. Therefore, we should immunize all CKD patients at high risk of progression, and seroconversion postvaccination should be assessed.

In conclusion, immunosuppression related to ESRD is profound and involves all the different components of the immune system, although the relative contribution of every cell type is not well defined. These alterations of the innate and adaptive immune system will only increase disease-attributable risk attributed to the primary disease, such as urinary tract infection in ADPKD patients.

## 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. 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. 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. 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. 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.

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 immunosuppression 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 transcriptome***

Previous 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. 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. 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. 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. 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. 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. 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. 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. 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 approach***

There 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. 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.

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. For ADPKD, a group from the United Kingdom has shown how a patient-centred approach may help to improve pain management in this cohort.

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. Hence, it has been recommended that research team leaders use real-world settings and seek advice from patients about which outcomes matter most.

**SUMMARY AND CONCLUSION**

CKD significantly shortens lifespan, partly due to increased rates of infection. The

likely cause is an altered immune status due to the chronic uremic milieu. Monogenic causes are a major contributor to adult CKD. In ADPKD, which is the most common genetic cause of CKD, patients are susceptible to specific bacterial pathogens once the disease has progressed. Here we argue that the application of emerging technologies such as scRNA-seq and dual RNA-seq to primary monogenic kidney diseases promises 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 (Figure 1).

Our approach has a number of limitations. ADPKD, while a major cause of ESRD, is not representative of the specificities of other causes of renal disease. Second, the interaction between uremia-induced immunodeficiency and infectious risk factors associated with the primary renal disease is difficult to model, and attributing a specific weight to each component requires a more complex analysis. Third, we focused on only a small percentage of novel tools with the potential to change our understanding of infections in ESRD patients. Nevertheless, our work remains relevant for its integration of state-of-the-art data from divergent disciplines, and its description of potential applications for the

improvement of infectious outcomes in renal disease merits further exploration.

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