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EDUCATIONAL REVIEW

Congenital anomalies of the kidney and urinary tract: defining risk factors of disease progression and determinants of outcomes

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Abstract

Congenital anomalies of the kidney and urinary tract (CAKUT) result from disruptions in normal kidney and urinary tract development during fetal life and collectively represent the most common cause of kidney failure in children worldwide. The antenatal determinants of CAKUT are diverse and include mutations in genes responsible for normal nephrogenesis, alterations in maternal and fetal environments, and obstruction within the normal developing urinary tract. The resultant clinical phenotypes are complex and depend on the timing of the insult, the penetrance of underlying gene mutations, and the severity and timing of obstruction related to the sequence of normal kidney development. Consequently, there is a broad spectrum of outcomes for children born with CAKUT. In this review, we explore the most common forms of CAKUT and those most likely to develop long-term complications of their associated kidney malformations. We discuss the relevant outcomes for the different forms of CAKUT and what is known about clinical characteristics across the CAKUT spectrum that are risk factors of long-term kidney injury and disease progression.

Keywords CAKUT · Kidney · Malformations · Nephrogenesis · Risk factor · Outcome

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are common in humans, encompassing 20–50% of birth defects with a collective prevalence of 4–60 per 10,000 live births. Neonates and infants with CAKUT are frequently subjected to radiologic and laboratory studies and referred for evaluation by pediatric nephrologists and/or urologists. In addition to defining the immediate impact of CAKUT, managing clinicians are often asked to project long-term kidney outcomes and to identify factors for risk mitigation. In this review, we address the embryonic origins of CAKUT, including the roles of genetics, intrauterine environment, and urinary tract obstruction. We discuss the clinical presentation of major forms of CAKUT, along with risk factors for adverse kidney outcomes and how to approach risk mitigation in pediatric nephrology practice. We make the argument that a variety of prenatal risk factors converge to reduce nephron number at birth. Following birth, certain patients with CAKUT develop acute kidney injury (AKI), which further reduces functioning nephron mass. Ultimately, it is the confluence of these factors—along with episodes of AKI postnatally—that determines the aggregate risk for poor kidney outcomes, including proteinuria, hypertension, and reduced glomerular filtration rate (GFR) (Fig. 1).

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The relationship of malformations to normal kidney development

Overview of normal human kidney development

Before discussing the scope of kidney malformation phenotypes that encompass human CAKUT, it is important to briefly highlight normal kidney development, as an interruption in any of these steps may lead to a kidney anomaly. Normal kidney development initiates in the first trimester

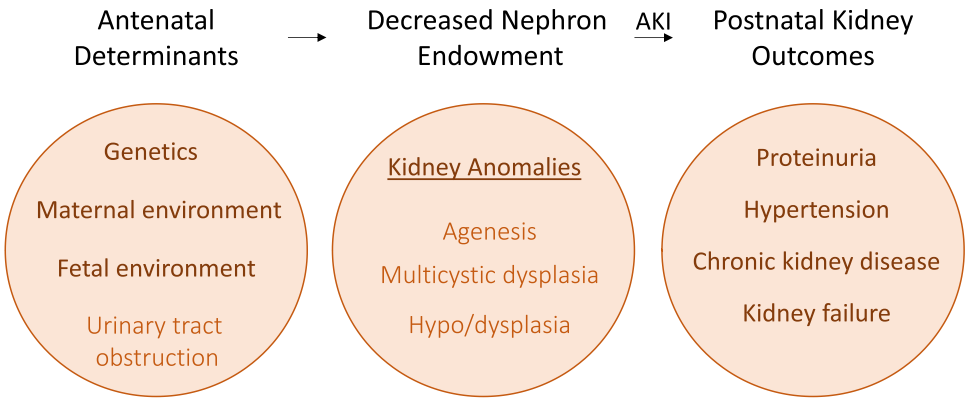

Fig. 1 Converging risk factors in the fetus (genetics, maternal–fetal environments, and urinary tract obstruction) lead to a spectrum of kidney anomalies that result in variable loss of functioning nephrons. This reduction in nephron endowment can be further eroded by episodes of acute kidney injury (AKI) after birth, leading to adverse kidney outcomes of proteinuria, hypertension, and reduction in GFR

with the sequential formation and involution of pronephros at 3 weeks of gestation and mesonephros at 4 weeks. The functional kidney arises from the metanephros during the fifth week when an outgrowth of the mesonephric duct—called the ureteric bud (UB)—invades the metanephric mesenchyme and undergoes a series of branching events. Signals from the tips of each branch and the mesenchyme cause the mesenchyme to epithelialize and forms a sequence of structures—pretubular aggregates, renal vesicles, comma- and S-shaped bodies—that ultimately give rise to the nephron, which consists of the glomerulus, proximal tubule, loop of Henle, and distal tubules. Signals from the mesenchyme promote further branching of the ureteric tree, which gives rise to the kidney collecting duct, pelvicalyceal system, and ureters. While the first glomeruli form during weeks 9–10, ureteric branching and nephrogenesis continue with an exponential increase during the late second and third trimester, concluding by 36 weeks. Fetal urine production commences at 11–12 weeks and accounts for > 90% of amniotic fluid by 16–20 weeks.

Kidney malformation phenotypes

Renal agenesis Congenital kidney and urinary tract malformations can arise at various points in this developmental sequence. As a general rule, lesions that occur earlier in development result in more severe anomalies. The most severe kidney anomaly is renal agenesis (aplasia), in which the UB fails to form or invade the mesenchyme. Mechanistically, this has been attributed to defects in growth factors and receptors that are critical for UB–mesenchymal crosstalk and survival of both lineages. This is exemplified by mutations in *GDNF* and *RET*, which encode a mesenchyme-derived ligand and UB-derived receptor, respectively [1, 2].

A series of inhibitory cues limit UB outgrowth to a single location, and the absence of these inhibitory signals can result in multiple UB—leading to partial or complete duplication of the kidney and/or collecting systems. In addition, the same molecular cues that guide UB outgrowth coordinate appropriate ureteral insertion into the bladder trigone, such that anomalies in these processes often co-exist. For example, complete duplication of the kidney collecting system can be associated with vesicoureteral reflux (VUR).

Dysplasia and hypoplasia Disruptions in nephrogenesis can result in dysplasia. While dysplasia generally is a clinical diagnosis supported by radiologic features, histopathologic studies in human fetal autopsies have established that dysplasia is typified by architectural distortion, metaplasia, primitive glomeruli and tubules, and cyst formation. Rodent studies have established that dysplasia can arise as a consequence of impaired UB–mesenchymal crosstalk and mutations in transcription factors [3]. A presumptive diagnosis is frequently made on the basis of an echogenic kidney with poor corticomedullary differentiation on kidney ultrasound, at times associated with cystic features. Renal dysplasia can present clinically with polyuria and electrolyte wasting with kidney functional impairment. In certain instances, dysplasia is associated with the presence of VUR.

When nephrogenesis proceeds in a normal fashion but yields low nephron numbers the resulting kidney is smaller (hypoplasia). This nephron deficit may be suspected based on kidney length if imaging is available (> 2 standard deviations below the mean for age). Alternatively, hypoplasia may be clinically silent and manifest later in childhood or even in adulthood in the form of proteinuria, hypertension, and impaired kidney function. These sequelae of hypoplasia are predicted by Brenner's famous hypothesis, which posits that low nephron numbers result in glomerular hyperfiltration and loss of podocytes [4], resulting in proteinuria and hypertension that can propagate glomerular injury and scarring and result in progression to kidney failure.

Genetic mechanisms underlying kidney malformations Classically, the role of genetic mechanisms in congenital kidney malformations was evinced by their association with chromosomal trisomy syndromes, i.e., + 18, + 13,

and + 21. Over the last 2 decades, studies in humans and mice have implicated a host of genes in kidney dysmorphogenesis. Current estimates are that 20% of kidney malformations have a monogenic origin [5], and another 4% may arise from copy number variants (CNV) that confer changes in gene dosage [6]. In the vast majority of instances, the nature and extent of kidney malformation phenotypes are variable among individuals inheriting the same genetic defect, illustrating the incomplete penetrance and variable expressivity that are common in human genetic disorders.

Role for genetic testing in patients with kidney malformations While there is insufficient evidence to broadly recommend genetic screening for all patients with kidney malformations, some have advocated that identification of a monogenic etiology can positively impact clinical management. For example, 5–15% of dominantly inherited kidney malformations have been attributed to mutations in *HNF1B* and *PAX2* [7]. Mutations in *HNF1B* have been associated with renal hypoplasia, hypomagnesemia, gout, and maturity-onset diabetes of the young (MODY). Alternatively, mutations in *PAX2* have been associated with impaired vision due to defects in the development of the retina and lens, as well as renal hypoplasia. These are examples of genetic conditions that if identified early can herald future complications allowing for anticipatory management. Moreover, successful identification of a genetic condition can lead to genetic counseling and inform future family planning. Some have advocated that genetic testing should be considered for patients with syndromic and severe kidney malformations on a case-by-case basis [8]. However, widespread genetic testing for kidney malformations is not currently performed as the standard of care in pediatric nephrology centers.

Influence of environment factors on kidney malformations While ongoing studies carry the promise of elucidating additional genes and pathways responsible for kidney malformations, most kidney malformations do not have an obvious genetic origin or familial pattern of inheritance. In this regard, it is important to consider that the maternal environment can significantly impact kidney development. Maternal malnutrition and placental insufficiency are both associated with low birth weight and prematurity, each of which is associated with low nephron number [9]. Maternal diabetes has been associated with kidney malformations in human and animal studies [10]. Increased maternal alcohol consumption can lead to fetal alcohol syndrome, including kidney malformations. A proposed mechanism is that competition between ethanol and retinol for metabolism via alcohol dehydrogenase can lead to fetal vitamin A deficiency. In this regard, it is noteworthy that vitamin A is a key morphogen for proper nephrogenesis, and vitamin A deficiency can lead to a nephron deficit [11]. Low maternal folate consumption is an established risk factor for neural tube defects as well as kidney malformations [12]. Maternal use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with renal hypoplasia [13], especially when taken in the second and third trimester when an exponential increase in nephrons normally occurs.

At this point in time, there are very few registries that report congenital kidney malformations, limiting their association with environmental exposures. An example of one such registry is the AGORA data in the Netherlands which has linked maternal obesity, maternal diabetes, and the use of assisted reproductive technologies—such as artificial insemination and in vitro fertilization—with kidney malformations [14]. While these associations may be limited by recall bias, they are foundational to identifying potential environmental links to kidney malformations, which can subsequently be explored at a mechanistic level.

Impact of fetal urinary tract obstruction on kidney development Urinary tract obstruction can occur at the ureteropelvic junction, ureterovesical junction, and bladder outlet. Obstruction can arise as a consequence of one or more discrete anatomic lesions (e.g., posterior urethral valves (PUV)) or a functional deficit in myogenesis or urinary tract innervation (e.g., Prune Belly syndrome (PBS)). The impact of urinary tract obstruction on kidney development varies tremendously. Studies in fetal sheep and monkeys have established that early obstruction leads to UB apoptosis and hypoplasia along with cystic dysplasia [15]. Conversely, obstruction that occurs later in gestation is less likely to result in dysplasia but can still result in renal hypoplasia and lead to kidney functional impairment after birth. Clinically, children born with obstruction that impacts both kidneys are more likely to have impaired kidney function. This occurs most often in boys with PUV, which result in bladder outlet obstruction and varying extents of renal dysplasia and hypoplasia.

Clinical Phenotypes of CAKUT

CAKUT represents a spectrum of disorders and, as mentioned, is the most common cause of chronic kidney disease (CKD) in children [16]. According to the UK Renal Registry, 40% of children on kidney replacement therapy have dysplastic or hypoplastic kidneys [16]. There are over 200 syndromes in which CAKUT is a component [17]. The phenotype of CAKUT ranges widely from generally benign conditions, such as mild transient hydronephrosis, to severe malformations, such as PUV with resultant kidney failure.

Antenatal diagnosis of hydronephrosis Many congenital kidney anomalies are brought to medical attention early in life due to advances in prenatal screening. In up to 5% of

pregnancies urinary tract dilation is noted prenatally; however, up to 80% of cases resolve spontaneously [17, 18]. Prenatal hydronephrosis reflects the wide variety of pathology seen within CAKUT and may be the presenting sign of a transient problem or more serious pathology. The ureter must effect peristalsis to move the urine into the bladder and delayed maturation of this smooth muscle may contribute to the transient hydronephrosis [16]. An antero-posterior kidney pelvis diameter (APD) of 7 mm or greater in the third trimester necessitates postnatal kidney ultrasound that should be performed after the first 48 h of life [18]. Unfortunately, not all cases of prenatal hydronephrosis represent a transient abnormality. In a study of 307 children at a tertiary care center in India, 80% of cases of CAKUT were detected prenatally with 70% of cases having prenatal hydronephrosis [19]. The postnatal follow-up may reveal additional pathology, with the most common findings being ureteropelvic junction stenosis or primary vesicoureteral reflux, but megaureter, duplex kidney, and PUV are also seen [18]. A meta-analysis conducted by Lee et al. reviewed case series published on antenatal hydronephrosis and analyzed data on 1308 patients that were diagnosed in utero based on APD and had postnatal outcomes reported. Of these patients, 36% had pathology confirmed during postnatal evaluation. The risk increased as the degree of antenatal hydronephrosis increased such that only 12% of patients with mild antenatal hydronephrosis (APD ≤ 7) had postnatal pathology, but 88% of patients with severe antenatal hydronephrosis (APD ≥ 10 mm) had pathology [20]. This study also highlighted the significant practice variation in the diagnosis and management of antenatal hydronephrosis and the need for a clinical practice guideline given the wide range of possible patient outcomes.

Upper versus lower urinary tract anomalies CAKUT can be divided into upper and lower urinary tract abnormalities. The most common types of upper urinary tract CAKUT conditions seen in the clinic include multicystic dysplastic kidneys, unilateral renal agenesis, and renal hypodysplasia. The most common congenital lower urinary tract obstructive lesions that impact kidney outcomes include PUV, urethral atresia, and PBS (Eagle Barrett syndrome) [21]. The definition, common imaging findings, and incidence of the different types of CAKUT are summarized in Table 1 [16, 17, 22]. Kidney imaging is the most common way to diagnose CAKUT.

The following section focuses on the definition, diagnosis, and prevalence of three of the most common CAKUT anomalies besides hydronephrosis: solitary functioning kidney, renal hypodysplasia, and urinary tract obstruction. This is followed by a general discussion of other CAKUT anomalies that typically do not have adverse kidney outcomes when present in isolation.

Table 1 Clinical phenotypes of CAKUT

Type of CAKUT	Common features within these categories	Kidney imaging findings	Incidence
Renal agenesis	Complete absence of one or both kidneys [22]	Absent kidney on RUS with no uptake of DMSA [16]. Solitary kidney often shows compensatory growth [17]	Unilateral 1 in 1000 to 2000 births, and bilateral 1 in 4000 births [22, 23]
Multicystic dysplastic kidney	Minimal or no kidney parenchyma with numerous cysts that do not connect and largest cyst is not central [22]	Postnatal RUS to confirm diagnosis, rule out ureteric obstruction, and evaluate the contralateral kidney [22]. DMSA scan will show no uptake in MCDK [22]	1 in 2200 to 4300 births [22, 23]
Renal hypo/dysplasia	Unilateral or bilateral involvement with varied kidney size. May be primary or secondary to other CAKUT [17]	RUS shows echogenic bright kidney with poor corticomedullary differentiation and decreased uptake on DMSA [16]	Unilateral 1 in 1000 births, and bilateral 1 in 5000 births
Prune Belly syndrome (Eagle Barrett syndrome)	Lower urinary tract has severe dilation but no true obstruction, deficiency of abdominal wall muscles, and cryptorchidism [16]	There is no "keyhole" sign on RUS	1 in 30,000 births [22]
Posterior urethral valves	Tissue leaflets within the prostatic urethra [18]	A bladder "keyhole" sign on prenatal ultrasound [22]. Definitive diagnosis by VCUG or endoscopy postnatally [22]	3.8–20 in 100,000 male births [22, 27]

CAKUT congenital anomaly of the kidney or urinary tract, *RUS* kidney ultrasound, *DMSA* technetium-99 m dimercapto succinic acid, *VCUG* voiding cystourethrogram

Solitary functioning kidney (SFK) The contralateral kidney of a multicystic dysplastic kidney (MCDK) and unilateral renal agenesis (URA) are the two forms of congenital SFK. MCDK occurs in up to 1/2200 to 1/4300 pregnancies and URA in 1/1300 to 1/2000 pregnancies [22, 23]. MCDK is a specific example of dysplasia, typically diagnosed by a kidney ultrasound showing hypoechogenic spaces due to multiple cysts of varying sizes which do not communicate with each other or the renal pelvis [16, 23]. A technetium-99 m dimercapto succinic acid (DMSA) scan will generally confirm no kidney uptake, however in about 4% of cases there may be minimal uptake representing 3–7% of function [16]. This residual function can increase the risk of hypertension and necessitate resection of the MCDK [22]. However, if there is no indication for early resection, when followed over time, an MCDK will typically regress due to cell apoptosis outweighing cell proliferation [16]. One-third of MCDK cases will involute by 2 years of age and over half will involute by 10 years of age [22]. MCDK is generally unilateral, and it is important to evaluate the contralateral kidney health as up to 40% will be abnormal and this dictates the long-term kidney prognosis [22, 23]. Low-grade VUR (grades I–III) is seen in about 25% of cases with other less common complications being uretero-pelvic junction (UPJ) or uretero-vesico junction (UVJ) obstruction, dysplasia, or severe reflux [22]. Evaluation with kidney imaging will confirm the diagnosis and a DMSA can confirm the kidney is non-functioning and rule out an ectopic kidney [16, 23].

Ultrasound imaging is also necessary to evaluate the solitary kidney of URA. This will assess for any malformations such as hydronephrosis, VUR, or UPJ obstruction and evaluate the kidney size which should be at least normal for age and ideally enlarged, representing compensatory hypertrophy. These are important predictors of long-term outcomes. There is currently a wide array of practice patterns and no guidelines on best practices for the management of patients with solitary function [24].

Renal hypodysplasia (RHD) Dysplasia of the kidney is due to abnormal differentiation or organization of the tissue, usually a consequence of an interruption of normal kidney development. Contrast this with hypoplastic kidneys that have a decreased number of nephrons but those present are formed properly [16]. Kidney ultrasound will typically identify a hypoplastic kidney by small size with fewer calices and papilla than expected [23]. Kidney biopsy is the only method to truly differentiate dysplasia from hypoplasia and this is generally not pursued in clinical practice [25]. Therefore, renal hypoplasia and renal dysplasia are grouped together as RHD. There are many varieties of a dysplastic kidney, which can range from unilateral to bilateral with kidney size that can vary from a small aplastic kidney to a large cystic kidney [16, 17]. The cysts of a dysplastic kidney form due to abnormal kidney development which results in the poorly differentiated tissue and primitive tubules [16]. This is in contrast to cysts arising from the pre-existing tubules in polycystic kidneys [16].

Urinary tract obstruction While a number of congenital urinary tract obstruction conditions occur as part of the CAKUT spectrum, including bladder outlet, bladder, and ureteric anomalies such as ureteropelvic junction or ureterovesical junction obstruction, children with PUV and those with PBS are most likely to develop CKD and kidney failure, and thus will be the focus of this section. PUV refers to redundant leaflets in the posterior urethra that can lead to partial bladder outlet obstruction with distended urinary bladder, bilateral hydronephrosis, VUR, and a spectrum of kidney involvement including dysplasia [26, 27]. PUV occurs in 3.8–20 per 100,000 live male births [22, 27]. Findings in utero of oligohydramnios with abnormal kidneys, a bladder that does not empty, a thick-walled megabladder with a "keyhole" sign, or urinary ascites from kidney or bladder rupture are all suggestive of PUV [18]. A multicenter study across five centers in the Pediatric Urology Midwest Alliance identified 274 patients with PUV over a 20-year period who had intervention for their disease within the first 90 days of life [28]. Of the 26% of patients who required kidney replacement therapy, one-third experienced rapidly declining kidney function in the first year of life as a likely consequence of dysplasia [21], while the remaining two-thirds experienced delayed progression between ages 10 and 15 years. While less common than PUV, PBS is another important cause of congenital urinary tract obstruction, occurring in 1 in 30,000 births [22]. Patients have a non-anatomic (functional) bladder outlet obstruction and varying degrees of urinary tract dilation, renal dysplasia, and kidney functional impairment. PBS is also associated with a deficiency of abdominal wall muscles, and cryptorchidism [16]. In PBS, as in PUV, recurrent urinary tract infections (UTI) and pyelonephritis are common and associated with the progression of kidney failure [29]. The mechanisms by which these infections occur and how they contribute to kidney injury have not been well described.

Other CAKUT anomalies There are several other CAKUT anomalies discovered over the course of antenatal screening or screening for some other reason (e.g., UTI, genetic syndromes, persistent/severe/complicated hydronephrosis). These include kidney ectopia, vesicoureteral reflux (VUR), and duplex kidney. These anomalies, when present in isolation and in the absence of recurrent UTI, are usually not associated with adverse kidney outcomes. However, a number of reports have shown that outcomes are worse in the conditions we have discussed (URA, MCDK, RHD, PUV) when they have these associated anomalies with or without

recurrent UTI. In fact, the presence of these associated anomalies has been shown to be an independent risk factor for chronic kidney injury [30, 31]. A discussion about these individual abnormalities and cystic kidney disease (which represents a broad spectrum of phenotypes) is beyond the scope of this report but they have been reviewed extensively elsewhere [16, 17, 32].

Defining CAKUT outcomes

Kidney outcomes in CAKUT Kidney outcomes studied among children with the different forms of CAKUT have included a number of standardized outcome measures (Table 2), including elevated blood pressure, proteinuria, a decrease in kidney function (such as a reduction in eGFR of 50%), and kidney failure (as defined by GFR < 15 ml/min/1.73 m^2 or starting kidney replacement therapy). These outcomes are not universally favorable and vary according to the type of kidney malformation. For example, the prevalence of chronic kidney injury in children with SFK has been reported to range from 0 to 45% [33, 34]; however, SFK is heterogeneous and includes children with MCDK and URA. As outlined in Table 2, in pooled estimates from 16 studies of MCDK, including a total of 1248 cases, a pooled median of 5.3% developed hypertension (range 0–20%), 15.2% developed proteinuria (range 0–29%), and 7.3% developed CKD (range 0–43%), over a mean follow-up of 5.9 years (range 2–10 years) [35]. In a report of kidney outcomes in URA, pooled estimates from nine studies showed that 16% of cases developed hypertension, 21% developed proteinuria, 10% developed CKD, with a median age of follow-up of 9.1 years [36].

There are few reports on the outcomes of CAKUT cases with RHD. Results from two studies demonstrated that up to 39% of cases developed hypertension, 25% developed proteinuria, 38% developed CKD, 12% developed kidney failure, with an age at last follow-up to 10.2 years [37, 38]. These estimates include data from the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial cohort, in which the inclusion criteria included above normal blood pressures and established CKD [37, 39]. The estimates for the outcomes are therefore likely closer to the lower end of the range quoted [38].

As previously discussed, PUV is the most common CAKUT lesion associated with childhood kidney failure. Not surprisingly then, as highlighted in Table 2, PUV is also more commonly associated with other chronic kidney injury outcomes when compared to the other categories of CAKUT. Based on a large body of published work, including a recent systematic review, up to 35% of PUV cases develop high blood pressure, 45% develop proteinuria, 22% develop CKD, and an astounding 37% develop kidney failure requiring kidney replacement therapy, including studies with a follow-up period of up to 31 years [28, 40–42]. Detailed long-term kidney outcome data for children with PBS are lacking; however, approximately 50% of cases in long-term follow-up reports have been shown to develop CKD or kidney failure (CKD Stage 5) (Table 2).

Risk factors for the progression of kidney disease In observational studies of adults with kidney disease, the progression of CKD has been used as a primary outcome measure, with diabetes, proteinuria, hypertension, and obesity used as traditional risk factors [43, 44]. Factors such as exposure

Table 2 CAKUT outcomes and risk factors for decline in kidney function

CAKUT category	↑BP (%)	↑UProt (%)	CKD (%)	CKD Stage 5 (%)	FU (yrs)	Risk factors	Refs
Multicystic dysplastic kidney[a]	5	15	7	–	5.9	genetic syndrome, kidney size, associated CAKUT, baseline eGFR	[35]
Unilateral renal agenesis[b]	16	21	10	–	9.1	genetic syndrome, kidney size, associated CAKUT, baseline eGFR	[36]
Renal hypodysplasia[c]	17–39	18–25	37–38	9–12	6.4–10.2	kidney size, hypertension, baseline eGFR	[37, 38]
Posterior urethral valves[d]	21–35	32–45	6–22[d]	15–37[d]	2–31[d]	oligohydramnios, nadir eGFR, kidney size, VUR	[28, 40–42]
Prune Belly syndrome	–	–	53	40–50	14.2	kidney size, nadir eGFR, pyelonephritis	[29]
Non-glomerular disease[e]	26	40	15	19	5.2	proteinuria, hypertension, CKD stage	[51]

CAKUT congenital anomaly of the kidney and urinary tract, *↑BP* blood pressure, *↑UProt* proteinuria, *CKD* chronic kidney disease, *FU* follow-up, *Refs* references, *eGFR* estimated glomerular filtration rate, *VUR* vesicoureteral reflux

[a]pooled estimate of 16 studies

[b]pooled estimate of 43 studies

[c]range of 2 studies (excluding PUV)

[d]range of median of 49 studies

[e]CKiD cohort

to nephrotoxins, acute kidney injury, fetal and maternal environment, genetic polymorphisms, and novel biomarkers are among the non-traditional risk factors and are less well-defined [45].

In contrast, risk factors for CKD progression in children and adolescents with kidney disease have not been well defined, given the lower incidence and prevalence of CKD than in adults. Earlier pediatric cohort studies, however, have identified a number of risk factors associated with childhood CKD progression, including baseline CKD stage [46], proteinuria [39, 47, 48], elevated blood pressure [49], and anemia [50], among others.

More recent large pediatric multicenter cohort studies have confirmed and refined these findings. In particular, the Chronic Kidney Disease in Children (CKiD) prospective observational study highlighted clinical characteristics that were associated with the outcome of reaching kidney failure, including proteinuria (urine protein to creatinine ratio greater than 2 mg/mg), hypoalbuminemia (serum albumin level less than 3.8 g/dl), and hypertension (systolic or diastolic BP greater than 95% for age, sex, and height) [46, 51]. Designed as an intervention trial in children with CKD, the ESCAPE trial showed the benefit of strict blood pressure control on the rates of developing the outcomes of kidney failure or a 50% reduction of GFR [37, 39]. Similar to CKiD, the ESCAPE trial identified high blood pressure, baseline GFR, proteinuria, and age at enrollment as risk factors for the composite outcome [37].

Risk factors for children with CAKUT While the CKiD and ESCAPE trial cohorts have helped identify risk factors for the progression of kidney disease in children with CKD, the application of their findings to specific risk factors in CAKUT cases is complicated by the heterogeneity of their inclusion criteria. The CKiD study stratified cases to glomerular and non-glomerular diseases, the latter being a heterogeneous mix of cases with CAKUT [52], while the ESCAPE trial stratified cases by glomerular disease and RHD, the latter a subgroup of all CAKUT categories. In addition, in both cohorts, only cases with established CKD were included, and in the ESCAPE trial those with higher blood pressure measurements. While these CKD cohort studies, like most adult CKD studies, have defined CKD progression as a primary outcome, CAKUT studies published to date have included hypertension, proteinuria, and the development of CKD or kidney failure, together or individually, as primary kidney injury outcomes. In cohorts with established CKD, where the cohorts are usually older in age, proteinuria and hypertension are used as risk factors. In cohorts where CAKUT is studied from birth and the cohorts are younger and CKD less prevalent, hypertension and proteinuria are often used as earlier kidney injury outcomes, alone or in combination with developing CKD or kidney failure. Risk factors for CAKUT cases associated with these outcomes have been described; those that are common to all CAKUT categories and that predict outcomes are less well defined, as summarized in Table 2. For CAKUT cases with an SFK (which includes MCDK and URA cases), an elevated serum creatinine at the time of diagnosis, a small SFK at diagnosis, structural anomalies in the SFK, and URA as the primary diagnosis have been associated with a worse long-term prognosis [31, 33, 35]. Risk factors for developing hypertension, proteinuria, or CKD progression in RHD cases have been less well described. Younger gestational age, smaller kidney size at diagnosis, a lower best estimated glomerular filtration rate (eGFR), proteinuria, and high blood pressure have been associated with the development of CKD, while kidney size at diagnosis has been shown to be an independent risk factor for kidney failure [38]. Developing CKD and kidney failure in CAKUT cases due to PUV has been well described [53]. The risk factors identified are similar to those of SFK and include nadir or baseline creatinine in the first year of life, proteinuria, and kidney parenchymal mass [54–57]. Previous reports have identified a number of other clinical characteristics associated with a poor outcome in these boys, including delayed diagnosis and surgical intervention [58], the presence of high-grade VUR [59], and impaired kidney function when evaluated postnatally at various times [60]. In addition, boys with PUV are prone to bladder dysfunction and recurrent UTI, and further studies are required to determine whether they constitute modifiable risk factors for CKD progression in this population.

Prediction models in CAKUT Common risk factors for the progression of disease across the different categories of CAKUT may exist but to date have not been delineated. The value of identifying these risk factors is their potential to predict prognosis and to lead to more personalized and cost-efficient long-term care [61]. However, most long-term kidney injury outcomes are complex and likely due to multiple factors. These factors may themselves be complex, some independently associated with the outcome, others can be confounding with their effect on the outcome influenced by the presence of the other factors, while others can be "lurking" variables which influence the outcome but have not yet been identified.

To help mitigate the confounding effects of multiple variables which may be important in determining outcomes, identified risk factors of outcome are best incorporated into a prediction model. Such models for the prediction of CAKUT outcomes are limited and a common model for all CAKUT cases has not been developed. In a clinical predictive model adjusted for most common clinical variables, proteinuria, hypertension, and baseline creatinine were shown to be independent predictors of CKD stage ≥ 3 in a single-center cohort of PUV cases [62]. Similarly, in a heterogeneous

cohort of SFK cases (which included cases of MCDK, URA, and RHD), baseline creatinine, recurrent UTIs, and kidney length were found to be independent predictors of a composite outcome consisting of hypertension, proteinuria, or CKD stage ≥ 3. Some of the challenges of developing single-center models like these include achieving adequate sample size to develop a robust statistical model as well as the need for validating the models in other centers, among others. They are, however, an important step in identifying and incorporating independent predictive variables into clinical care algorithms.

Care of the child with CAKUT in the nephrology clinic

Identifying clinical characteristics that predict kidney outcomes enables the development of evidence-based, risk-stratified pathways for the care of children with CAKUT. Such pathways can direct resources toward children most at risk for developing complications while directing low-risk patients toward care by primary care providers. High-risk patients can be further stratified based on a weighted risk to inform the frequency and intensity of care in multidisciplinary CKD clinics that provide comprehensive support to the patient and their caregivers. Studies of adult CKD patients have shown an increased time to dialysis when a multidisciplinary care clinic model is implemented and in pediatric pre-dialysis CKD patients it has been shown to decrease the rate of disease progression and length of hospital stay as well as improving management of other aspects of CKD such as anemia [63]. Psychosocial and educational services are essential facets of the healthcare for children with CKD. In a study comparing pre-dialysis pediatric CKD patients, 50% of whom have CAKUT as their primary kidney diagnosis, with age-matched controls, despite a similar level of resilience the patients with CKD had significantly lower health-related quality of life and higher amount of grade retention and interrupted studies [64]. Additionally, nutrition support should be integrated to allow for biannual screening of all patients with CKD stage 3–5 by a registered dietician and for incorporation of dietary modifications which have been shown to decrease the progression of kidney disease [65]. Multidisciplinary clinics vary widely in composition with most having a nephrologist, nurse, and dietician, but only about half incorporating social work and less than half have dedicated pharmacy support [66]. Furthermore, multidisciplinary clinics benefit tremendously from partnerships between nephrologists and urologists, who can guide the prevention and management of bladder dysfunction, urinary tract obstruction, and UTI that arise in certain patients with CAKUT. Unfortunately, despite the knowledge that outcomes are improved with this comprehensive care model, the optimal entry point and structure of such clinics has not yet been established and there has been little analysis of the pediatric CKD population in general, and of cases with CAKUT specifically, on best practices for improving outcomes [66].

Summary points

1. CAKUT can arise as a consequence of genetic determinants, maternal nutritional deficiencies, fetal environmental exposures, or urinary tract obstruction.
2. Kidney malformations that result in low nephron mass can lead to hypertension, proteinuria, reduced GFR, and CKD progression toward kidney failure.
3. CAKUT is a broad spectrum of diseases that have significant variation in presentation, severity of malformation, and outcome, necessitating a way to risk stratify patients for the decline in kidney function.
4. Among types of CAKUT, PUV is associated with poor kidney outcomes, particularly when accompanied by RHD.
5. Multidisciplinary clinics have been shown to benefit patients with CKD, but the optimal implementation of this practice model has not been identified.

Multiple choice questions

Answers are given following the reference list.

1. Identified risk factors for the development of chronic kidney disease in children with CAKUT include

   a) the underlying CAKUT diagnosis
   b) kidney size
   c) baseline eGFR
   d) family history of CAKUT
   e) a, b, and c
   f) all of the above

2. The specific CAKUT category most likely associated with the long-term outcome of kidney failure is

   a) multicystic dysplastic kidney
   b) unilateral renal agenesis
   c) renal hypodysplasia
   d) posterior urethral valve
   e) none of the above

3. A term newborn in the level 1 nursery was found to have antenatal hydronephrosis on a third-trimester ultrasound with an APD of 12 mm. What is the next best step in management?

   a) Refer to Nephrology for appointment within the first month of life
   b) Monitor urine output prior to discharge home
   c) Obtain kidney bladder ultrasound at 48 h of life
   d) Schedule patient for VCUG
   e) Urgent referral to Urology

4. Essential components of a successful multidisciplinary pediatric CAKUT care team include

   a) pediatric nephrologist
   b) specialty nurse
   c) social worker
   d) dietitian
   e) pharmacist
   f) geneticist
   g) psychologist
   h) all of the above

Declarations

Competing interests The authors declare no competing interests.

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Answers: 1: e, 2: d, 3: c, 4: h

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