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Review Article

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Predictive Factors of Chronic Kidney Disease Risk in Childhood Urinary Tract Infection

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ABSTRACT

This narrative review presents a conceptual framework exploring the relationship between urinary tract infections (UTIs) in children and the risk of chronic kidney disease (CKD) later in life. It highlights predictors of CKD risk and critically examines the evidence for the pathophysiologic pathways linking UTI with CKD. The clinical implications for preventive nephrology are also discussed. The conceptual model for predicting CKD risk from previous episodes of childhood UTI is based on several pathophysiologic pathways. Although the pathophysiologic pathways may include UTI-associated kidney scars and co-existing risk factors for recurrent UTIs like dysfunctional elimination syndrome, high-grade vesicoureteral reflux (VUR), and congenital anomalies of the kidneys and urinary tract (CAKUT), the VUR-UTI-kidney scar-CKD trajectory is currently debatable. Recent evidence-based data suggest that the occurrence of new kidney scars is associated with the presence or absence of UTIs in infants with high-grade VUR, thus challenging the traditional VUR-UTI-kidney scar-CKD paradigm. Most episodes of UTIs do not lead to future CKD if infections are promptly treated and underlying VUR and CAKUT are appropriately managed. Some indirect and direct predictors of CKD risk include demographic factors like young age of incident UTIs and female sex, duration or presence of high-grade VUR, severity of kidney scarring,andmicroalbuminuria. Some of the modifiable predictors that potentially accelerate CKD progression should be targeted by kidney-protective strategies, such as managing VUR, screening for functional risk factors for CKD, or risk markers (e.g., microalbuminuria), and applying pharmacologic or surgical interventions to mitigate these risk factors.

Keywords: Child, chronic kidney disease, kidney scarring, urinary tract infection, vesicoureteral reflux

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INTRODUCTION

Urinary tract infection (UTI) places a high morbidity burden in children.[1] The clinical types comprise febrile UTIs (acute pyelonephritis or upper tract UTI), afebrile UTIs (cystitis or lower tract UTI), and recurrent UTIs.[2] The UTI can also be uncomplicated or complicated; the latter occurs with structural or functional urinary tract anomalies, or a compromised immunity, predisposing to antimicrobial resistance and increasing the risk of more complications like kidney damage or urosepsis.[3] Recurrent UTI is defined as 2 or more episodes of UTI in 6 months or 3 episodes within 12 months.Recurrence or improper treatment of UTI may have severe consequences for long-term kidney function. Specifically, recurrent UTI is potentially associated with kidney scarring, and subsequent hypertension and chronic kidney disease (CKD), including kidney failure with the need for kidney replacement therapy (KRT).[4]

Approximately 15% of pediatric patients with first UTI will show imaging evidence of kidney scarring, a structural predictor of CKD risk.[5] After febrile UTIs, 30%-40% will likely develop the same complication, independent of other co-morbid structural anomalies

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like congenital anomalies of the kidney and the urinary tract (CAKUT) and primary vesicoureteral reflux (VUR).[6] Many children with UTIs, including recurrent UTIs, do not end up with CKD if the infections are promptly treated and the underlying structural anomalies are managed. However, some authors have challenged the notion associating post-UTI kidney scarring with hypertension and CKD because there is scanty evidence to suggest that kidney scarring depends solely on UTI episodes.[7]

A recent retrospective cohort study reported a low prevalence of kidney scarring in an unselected population of children exposed to UTI before the age of 5 years, suggesting that UTI was not associated with CKD, hypertension, or kidney failure by the age of 10 years.[8] The authors thus recommended the need for longer follow-up to ascertain if UTI is associated with subsequent kidney complications without co-existing risk factors.[8] Interestingly, a recent randomized, open-label trial suggests that the occurrence of new kidney scars was not associated with the presence or absence of UTIs in infants with high-grade VUR.[9] The authors' finding contradicts the practice of routine continuous antibiotic prophylaxis in infants with high-grade VUR aimed at preventing UTI and the long-term sequelae associated with kidney scarring, such as CKD risk.

This narrative review discusses a conceptual framework on whether UTIs in children are related to CKD risk later in life. It highlights the predictors of CKD risk and critically examines the evidence for the pathophysiologic pathways linking UTI with CKD. The clinical implications for preventive nephrology are also discussed.

MAIN POINTS

- Although kidney scarring may complicate recurrent urinary tract infections (UTIs) or acute pyelonephritis, the role of childhood UTIs in the long-term development of chronic kidney disease (CKD) risk is currently a contentious issue. However, kidney scarring is known to be accentuated in the presence of underlying urologic abnormalities such as vesicoureteral reflux (VUR) or congenital anomalies of the kidneys and urinary tract (CAKUT).
- Some predictors of CKD risk in children with UTIs include patient demographic variables (younger age and female sex),presence or duration of VUR, high-grade VUR, bilateral or previous kidney scarring,andmicroalbuminuria. Nevertheless, recent evidence-based data have challenged the VUR-UTI-kidney scar-CKD paradigm, casting doubts about the role of childhood UTI in the long-term complication of CKD risk.
- The CKD progression to late stages (G5) can be accelerated by functional risk factors (hypertension), structural risk factors (VUR), and risk markers (microalbuminuria). Kidney-protective strategies, like pharmacologic and surgical interventions, can help mitigate these risk factors and markers.

Childhood Chronic Kidney Disease: Definition and the Common Etiologic Factors

Chronic kidney disease is defined as abnormalities of kidney structure or function for greater than 3 months, with health implications, and is classified based on cause, glomerular filtration rate (GFR) category (G1-G5), and albuminuria (A1-A3).[10] To achieve the goal of early commencement of effective therapy, the Kidney Disease Outcomes Quality Initiative working group of the National Kidney Foundation defined CKD (applicable for children older than 2 years of age) as "evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies, or histology) that persist for at least 3 months, with or without a decreased GFR, as defined by a GFR of less than 60 mL/min per 1.73 m^2."[11]

Within the past decade, kidney registries and cohort studies of childhood CKD and kidney failure show that CAKUT remains the most common etiologic factor, with hypertension and albuminuria constituting the independent risk factors for CKD progression.[12] Obstructive uropathy is another common cause of CKD in children.[13] It can result from posterior urethral valves in male children, bladder outlet obstruction from neurogenic bladder, ureteropelvic junction obstruction, ureterovesical junction (UVJ) obstruction, and primary VUR. Chronic obstruction from these structural and functional causes leads to progressive hydronephrosis and potential kidney scarring from reflux nephropathy. Again, these structural and functional anomalies (especially CAKUT and VUR) can cause urinary stasis, driving incident UTI or recurrent UTIs that increase the likelihood of chronic kidney scarring and direct reduction of nephron reserve. The reduced nephron reserve may result in CKD risk, given the failure of kidney compensation during growth.[14] For instance, in the critical window of kidney development (birth to 2-3 years), UTIs may outstrip the impact of nephron reserve if CAKUT is present. In contrast, from adolescence to adulthood, long-term CKD risk is more likely if early kidney scarring is significant. In middle childhood (4-12 years), recurrent UTIs may accentuate the risk for kidney scarring, necessitating close monitoring and intervention for drivers of CKD such as hypertension.

Is Post-Urinary Tract Infection Kidney Scarring a Structural Predictor of Chronic Kidney Disease Risk?

The conventional opinion is that the triad of childhood UTI, VUR, and permanent kidney scarring can lead to CKD risk in the second or third decade of life. More importantly, UTI appears to be a warning sign for the presence of underlying urinary tract anomalies such as CAKUT and VUR. Although ^{99m}Tc-DMSA scintigraphy has identified kidney scarring in a substantial percentage of children after febrile UTI independent of VUR, both primary and secondary VUR are important risk factors for post-UTI kidney scarring.[15] This observation further underscores the role of other factors in predisposing children with UTI to future CKD risk independent of VUR alone[7,16] Nevertheless, there are some limitations of the ^{99m}Tc-DMSA scintigraphy for kidney scar diagnosis in children, and these include its poor spatial

resolution leading to missed or obscured lesions, its limited ability to distinguish acute pyelonephritis from kidney scarring, and its inability to differentiate between congenital and acquired kidney scars caused by CAKUT (especially kidney dysplasia) and UTI, respectively.[17]

A conceptual risk-stratification model identifies CKD risk categories as not directly based on UTI type and CAKUT, but rather on a complex interplay of factors, where certain UTI types and CAKUT increase the risk of CKD. Lower urinary tract obstruction and anomalies can predispose to complicated UTI, which subsequently can exacerbate kidney damage and accelerate CKD progression. Notably, CKD risk is basically determined by GFR and the presence of kidney damage (like proteinuria or structural anomalies) rather than a direct role of the UTI type. Although UTIs can accelerate CKD progression with existing kidney disease, especially at stages G3-G5, it is trite to emphasize that they are not a primary risk factor for initiating CKD. The presence of co-morbid structural abnormalities, such as VUR (confirmed by imaging along with evidence of kidney damage), leads to CKD risk and guides management, with high-grade VUR suggesting greater CKD risk.[18] The CKD risk categories thus include low risk (isolated, uncomplicated afebrile UTI with standard imaging, without urinary tract anomalies), moderate risk (febrile UTI with dysfunctional elimination syndrome, mild VUR or hydronephrosis on imaging), and high risk (recurrent febrile UTIs, presence of CAKUT with high-grade VUR, kidney scarring on imaging).

The proposed pathophysiologic pathways linking childhood UTI to CKD risk are as follows. The UTI elicits an inflammatory response in the kidney (pyelonephritis risk), which may result in acute kidney injury (AKI) and kidney scarring. The structural changes in the kidney (kidney scarring) with nephron loss lead to altered hemodynamics, such as hypertension and hyperfiltration. The CKD then develops over time. Some modulating factors can amplify or attenuate each process, resulting in varying degrees of CKD risk. For instance, the presence of CAKUT/VUR amplifies these processes, resulting in a higher risk of CKD, while prompt antibiotic treatment attenuates the processes and lowers CKD risk. Better still, kidney scarring follows recurrent febrile UTIs or pyelonephritis. Kidney scarring, especially in the papillae, reduces nephron number and function over time. Whereas CAKUT or VUR increases the risk of recurrent UTI and potential kidney scarring, dysfunctional elimination syndrome is associated with incomplete emptying and higher residual urine volumes, which promote recurrent UTI episodes. The subsequent kidney scarring may trigger compensatory or adaptive hyperfiltration in the remaining nephrons, accelerating CKD progression. Adaptive hyperfiltration refers to a compensatory GFR rise in the remaining normal nephrons. The elevated GFR ultimately leads to long-term glomerular injury, which eventually manifests as varying degrees of albuminuria and progressive decline in GFR (CKD). The CKD can deteriorate into late categories like G4 and G5 (especially kidney failure), with the presence of secondary factors: albuminuria, systemic or intraglomerular hypertension, hyperphosphatemia, anemia, metabolic acidosis, and tubulointerstitial disease[19] (Figure 1).

Regarding predictors of CKD risk, there is still a lack of unanimity about the role of childhood UTIs in the long-term development of CKD.[7] However, several studies have tried to explore this unclear CKD risk in selected populations of children with severe UTI or underlying risk factors such as VUR, as well as in unselected populations (Table 1). In a retrospective population-based cohort study using linked GP, hospital, and microbiology records in the United Kingdom, Hughes et al[8] evaluated the relationship between UTIs and kidney outcomes in an unselected population of children. The authors used children born between 2005 and 2009 as study participants, whom they followed up for 8-12 years. The exposure was culture-proven UTI before the age of 5 years, and the key outcomes were kidney scarring, hypertension, CKD, and kidney failure. The authors found a preponderance of female subjects, of whom 7% had UTI before the age of 5 years, but a low prevalence rate of kidney scars. However, the odds of kidney scarring appeared higher in children with UTI by the seventh year of life. The study concluded that in the absence of underlying risk factors such as VUR or CAKUT, UTI was not associated with CKD, hypertension, or kidney failure by the tenth year of life. The authors thus recommended a longer follow-up to establish whether UTI is subsequently associated with these outcomes, particularly in the absence of these additional risk factors. Their findings align with those of other authors who suggested young age and female sex as patients' demographic factors influencing the incidence of post-UTI kidney scarring.[16] Permanent kidney scar formation reportedly occurs in 15%-60% of children after UTI episodes.[20] Similarly, a prevalence of 31% was noted in Iranian children, while its prevalence in children with VUR was about 4 times higher than that of their counterparts without VUR.[21] The disparities in prevalence rates are, however, attributed to different study sample sizes and variations in age and sex distributions, VUR grade, and co-morbid urologic anomalies.[22] Hitherto, VUR was generally considered the most significant risk factor for post-UTI kidney scar formation in children. Lee et al[23] even concluded that VUR was the sole independent risk factor for kidney scarring after febrile UTI in infancy, as VUR severity was significantly associated with the risk of permanent kidney damage. These findings were corroborated by Bundovska-Kocev et al,[24] who observed that longer duration of VUR diagnosis, microalbuminuria, and bilateral kidney scarring were predictors of CKD risk. The authors thus recommended that UTI with co-morbid primary VUR should warrant a patient's long-term assessment for CKD up to the second and third decades of life.In contrast, Gordon et al[25] reported VUR as a weak predictor of kidney injury in children hospitalized with UTI, after conducting a systematic review and meta-analysis to establish how the finding of primary VUR on voiding cysto-urethrogram (VCUG) in children hospitalized with UTI predicted CKD risk on ^{99m}Tc-DMSA

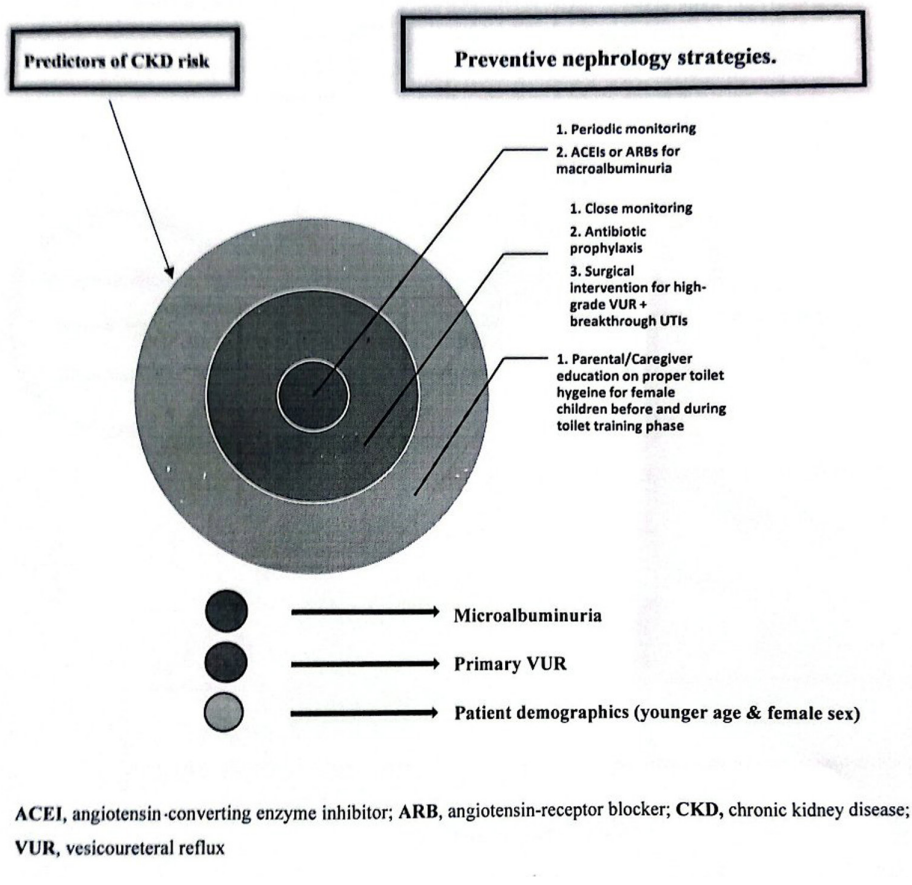


Figure 1. Schematic diagram illustrating the urinary tract infection-vesicoureteral reflux-chronic kidney disease pathophysiologic pathway.

scintigraphy.They found that a positive VCUG increased the likelihood of kidney injury risk in hospitalized UTI patients by about 20%, whereas a negative VCUG increased the likelihood of non-involvement of the kidneys by only 8%. It may not just be the presence of VUR that predisposes to post-UTI kidney scarring but the duration of this urologic abnormality,[24] and the presence of other underlying factors.[7,16] Thus, in this selected population, there appears to be a limitation in using VCUG-detected primary VUR to effectively screen for CKD risk, as the pathogenesis of kidney injury may be complex given its frequent detection without demonstrable VUR.[25] For instance, some authors have observed permanent kidney scar formation in many infants without VUR, and have therefore suggested the role of other risk factors such as bacterial virulence, host defense factors, and genetic susceptibility in kidney scarring.[23] Although several authors hold the belief that UTI and VUR constitute the causes of kidney scarring, the exact pathogenesis of post-UTI kidney scarring is not entirely understood and is being challenged. Specifically, it is now thought that reflux nephropathy is not always acquired and secondary to UTI but may point to reflux-related damage associated with congenital dysplastic kidneys.[26] Some authors also suggest that reflux nephropathy may actually be a component of CAKUT, thus shifting the paradigm of the latter from the anatomic conceptual model.[27]

A recent randomized, open-label, multicenter trial in a selected population of infants with high-grade VUR further provides another perspective that directly challenges the traditional VUR-UTI-kidney scar-CKD paradigm. In the PREDICT trial, Morello et al. assessed whether continuous antibiotic prophylaxis would be effective in preventing the occurrence of a first symptomatic UTI and would mitigate future kidney damage in infants with high-grade VUR and no previous UTIs.[9] After 2 years of prophylactic antibiotics in these infants aged 1-5 months, the authors compared the primary outcome (first symptomatic UTI) and secondary outcomes (e.g., new kidney scars) between the prophylaxis group and the untreated group. They found that a first symptomatic UTI occurred in 21.2% of the trial participants in the prophylaxis group and in 35.6% in the untreated group. Additionally, the authors noted that the number of new kidney scars was independent of the occurrence of UTIs during the trial period, and that participants with CAKUT at baseline were not at greater risk for UTIs during the 2-year follow-up. These findings corroborate previous observations that showed no mitigation of kidney scarring despite the effectiveness of antibiotic prophylaxis in preventing UTIs.[28,7] These evidence-based data not only contradict the practice of antibiotic prophylaxis in children with VUR but also cast doubts about the VUR-UTI-kidney scar-CKD trajectory.

Table 1. Primary Studies and Systematic Reviews Reporting Predictors of Chronic Kidney Disease (CKD) Risk

Study Authors (Year of Publication and Country of Study/Systematic Review)	Study Design	Study Method	Predictors of CKD Risk
Hughes et al[8] (2024, the United Kingdom)	Retrospective population-based cohort study	• Linked GP, hospital, and microbiology records of children born 2005-2009, followed up for 8-12 years • Culture-proven UTI <5 years as study exposure, kidney scarring, hypertension, CKD, and kidney failure as outcomes	• Female sex [§] • Young age (<5 years)[†§]
Bundovska-Kocev et al[24] (2019, Macedonia)	Longitudinal study	• Evaluation of the records of 101 children who had UTI and VUR • Interviewing them at 8-32 years from the first episodes of VUR, and determining their kidney function using eGFR	• Longer duration of VUR diagnosis§ • Microalbuminuria ± Bilateral kidney scarring±
Gordon et al[25] (2003, the United Kingdom)	Systematic review/meta-analysis	• A search of the Medline, Embase, and PubMed electronic databases for reports on primary data for hospitalized children with culture-proven UTI who had undergone both VCUG and ^{99m}Tc-DMSA scintigraphy	VUR*[§]
Soylu et al[29] (2008, Türkiye)	Retrospective hospital-based study	• Assessment of the association of sex, age, and VUR grade with preformed kidney scarring	• Male sex[§] • Age ≥27 months in females[§] • Grades IV-V VUR[§]
Salo et al[4] (2011, Finland)	Systematic review	• Systematic literature search on the association between childhood UTIs and CKD, and review of the data for patients with CKD	• Recurrent UTIs*[§]
Ditchfield et al[30] (1994, Australia)	Prospective cohort study	• Prospective evaluation of 193 consecutive patients aged <5 years old, seen at the ambulatory pediatric department during 3 years, and who had a first culture-proven UTI	• Age <2 years[§] • VUR[§]
Shaikh et al[20] (2010, United States)	Systematic review	• A search of the Medline and Embase databases and inclusion of articles if they reported data on the prevalence of abnormalities on acute-phase (≤15 days) or follow-up (>5 months) in children aged 0 to 18 years after an initial UTI	• VUR (grades III or higher)[§]

[†]Absent underlying risk factors for post-UTI kidney scarring.
*A weak predictor of CKD risk.
[§]Indirect predictor
[±]Direct predictor.
eGFR, estimated glomerular filtration rate; GP, general practice; UTI, urinary tract infection; VUR, vesicoureteral reflux; VCUG, voiding cysto-urethrogram; ^{99m}Tc-DMSA, 99mTc-labeled dimercaptosuccinic acid.

Despite the discordant opinions about the VUR-UTI-kidney scar-CKD trajectory, other reports emphasize the possible validity of this pathophysiologic concept. For instance, a retrospective study in Türkiye by Soylu et al[29] assessed the relationship between demographic factors and VUR grade with preformed kidney scars, as well as the association between demographic factors, VUR grade, presence of preformed kidney scars, number of breakthrough UTIs, and VUR resolution with new kidney scar formation. They found that the indirect predictors of CKD risk among children presenting with a UTI were male sex, age ≥27 months in females, and high-grade VUR. In contrast, a direct CKD risk predictor was the presence of a previous kidney scar.[29] The finding of male sex as an independent indirect predictor of CKD risk is at variance with previous observations which suggested female sex.[8,16] It is speculated that the possible preponderance of uncircumcised males in the study setting of Soylu et al[29] might have increased the odds for recurrent UTIs among the male subjects, since male circumcision status and high-grade VUR are known putative risk factors for recurrent UTI which is traditionally thought to predispose to kidney scarring.A systematic review by Salo et al[4] which determined the etiologic fraction of UTIs that led to CKD risk found that only 13 of the 58 patients with infectious causes of CKD had a history of UTIs in childhood. In their initial imaging studies, all 13 patients presented with abnormalities in their kidney tissue. They noted that recurrent UTIs were possibly the cause of

CKD in only 1 case, buttressing the previous observation that children with normal kidneys (i.e., absence of CAKUT) are not at significant risk of developing CKD because of UTIs. Also, other authors in Australia who conducted a prospective cohort study in children after their first culture-proven UTI sought to determine the relationship between kidney scars, demographic factors, the presence and grade of VUR, and infective organism.[30] They found a greater prevalence rate of kidney scars in patients aged <2 years old than in their older counterparts (33% vs. 17%), as well as a higher prevalence rate in those with VUR compared to those without it (45% vs. 24%).Furthermore, VUR was absent in 63% of kidneys with kidney scarring, as there was no established association with sex or infective organism. Thus, the authors concluded that whereas early kidney scars were associated with VUR and an age <2 years, a significant proportion of these lesions occurred in the absence of VUR, thus downplaying the presumed role of VUR in kidney scar formation. Finally, the systematic review by Shaikh et al[20] assessed the prevalence of acute and chronic kidney imaging abnormalities in children after an initial UTI.The authors reported that 57% of the children had changes consistent with acute pyelonephritis on acute-phase ^{99m}Tc-DMSA scintigraphy. In comparison, 15% had evidence of kidney scarring on follow-up scintigraphy. Additionally, children with VUR were significantly more likely to develop pyelonephritis and kidney scarring compared with children without VUR. Specifically, children with high-grade VUR were more likely to develop kidney scarring than children with low-grade VUR,[20] which is a confirmation of the previous observation about the correlation between VUR severity and kidney scar formation.[29]

Chronic Kidney Disease Risk Predictors: Implications for Preventive Nephrology

Preventive nephrology aims to minimize the incidence of kidney failure in children and the need for KRT through proactive strategies, as well as improve the patient's quality of life through early detection and management of CKD. Some of its fundamental principles include identifying risk factors for CKD; identifying early categories of CKD (G1 and G2) through screening for blood pressure (BP), serum creatinine, estimated glomerular filtration rate (eGFR), and albuminuria; patient/caregiver education on kidney health and risk factors for kidney disease; and managing underlying conditions contributing to CKD risk. Two key proactive or preventative pharmacology-based strategies comprise BP control to slow down CKD progression and treating albuminuria using an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin-receptor blocker (ARB) to protect kidney function. In the present narrative review, some predictive factors of CKD risk include patients' demographic variables such as age and sex,[8,16,28,30] presence or duration of VUR or higher grade VUR,[4,8,20,24,25,29] bilateral or previous kidney scarring,[24,29] and microalbuminuria.[24]

Whereas there appears to be a consensus on the young age of incident UTI as an indirect predictor of CKD risk, there is no unanimity about the role of sex. Nonetheless, applying the principles of preventive nephrology to these patients' demographics will involve avoiding UTIs in male and female children early in life through parental or caregiver education on risk-factor mitigation. For instance, clinicians and health professionals should educate parents and caregivers on proper toilet training and anal cleaning habits (especially in the female child), and the beneficial role of early male circumcision. Despite studies that reported lower incidence of UTI in circumcised males compared to their uncircumcised counterparts,[31, 32] another study suggested that the observed differences in UTI rate by circumcision status were entirely due to sampling and selection bias.[33] The latter believes that circumcision should not be recommended as a preventive strategy for UTI unless sources of bias are well controlled for in research studies.[33] However, evidence-based data suggest that circumcision changes the peri-urethral uropathogens to a preponderance of skin commensals, thus reducing the likelihood of UTI.[34] These reports form the basis for recommending post-natal male circumcision as a preventive strategy for UTI. Again, the direct bacterial invasion of kidney parenchyma in febrile UTIs triggers an inflammatory response which can cause significant long-term kidney damage; hence, making prompt diagnosis and commencing appropriate treatment are crucial to prevent or minimize complications like kidney scarring, a predictor of CKD risk.[35] Similarly, corticosteroids (like dexamethasone) can be used as an adjunctive treatment with antibiotics for febrile UTIs to suppress the inflammatory response and thus mitigate kidney scar formation.[36]

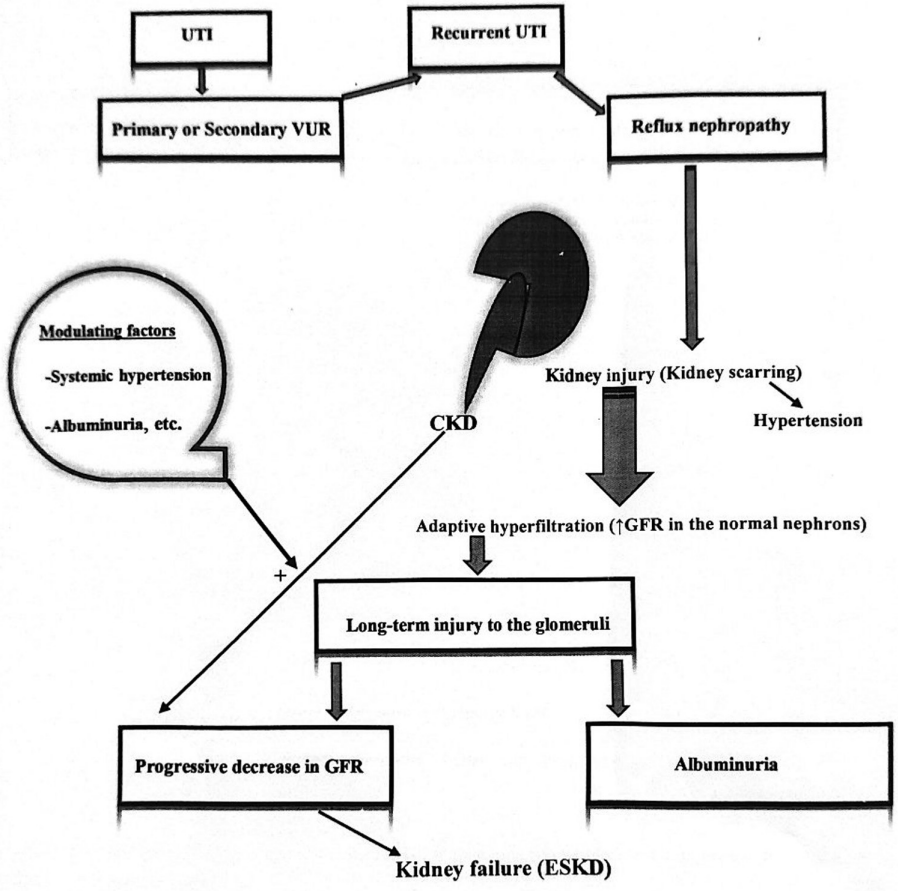
Secondly, managing underlying conditions that predispose to CKD is an essential principle in preventive nephrology. Thus, treating primary VUR is a crucial strategy to obviate CKD risk. However, multifactorial considerations drive the management of VUR, which may include only close monitoring or prophylactic antibiotics, as few patients (especially those with breakthrough febrile UTIs) would require surgical intervention.[37] For instance, the current evidence-based clinical practice guideline from the Indian Society of Pediatric Nephrology for the management of UTI and primary VUR in children recommends that prophylactic antibiotics are not indicated in children with a normal urinary tract after a UTI episode, but may be indicated in those with dysfunctional elimination syndrome and high-grade VUR.[38] Also, surgical intervention for high-grade VUR can be recommended for parental preference over prophylactic antibiotics, or in children placed on prophylactic antibiotics who develop recurrent breakthrough febrile UTIs.[38] Regarding patients with kidney scars and significant kidney scars (i.e., bilateral kidney scars), hypertension and albuminuria, respectively, should be monitored as part of the proactive approach to preserve kidney function. Although hypertension (which occurs in 10%-30% of children and young adults with post-UTI kidney scarring) may develop after 8 years,[39] its precise etiopathogenesis is unknown. However, it is speculated that this results from segmental ischemia with increased renin secretion and is not dependent on the severity of kidney scarring.[14] For children

with non-glomerular causes of CKD, albuminuria is only seen with kidney scarring in later stages of CKD.[40] Again, persistent proteinuria (urine protein-creatinine ratio of >2) predicts significant progression of CKD, besides other modifiable risk factors like hypertension, obesity, and AKI, as well as non-modifiable factors like low nephron number, genetics, and CAKUT.[41]

Finally, microalbuminuria is a recognized predictor of CKD risk and serves as an early indicator of kidney injury, also signifying the potential progression of CKD to kidney failure. Additionally, combining eGFR and microalbuminuria to classify CKD improves its predictive value for kidney failure (CKD-G5).This finding supports the notion that microalbuminuria is currently regarded as a risk marker for cardiovascular events and CKD rather than a risk factor.Better still, its presence alone is not an indicator of CKD, especially if the eGFR is >60 mL/min/1.73 m^2. Microalbuminuria should be monitored for progression to albuminuria: a risk factor for progressive loss of kidney function. Optimal reduction of albuminuria with ACEIs or ARBs should, therefore, be the target of any kidney-protective intervention (Figure 2).

Gaps in Knowledge and Future Research

The multiple non-infectious factors (such as hypertension, AKI, and obesity) contributing to childhood CKD progression are already established. Similarly, infectious diseases in CKD patients appear to increase the risk of CKD progression. For instance, children with febrile UTIs are at risk of kidney scarring (a CKD risk factor), while those with neurogenic bladder have an increased risk of rapid progression to late CKD stages after recurrent UTIs. However, the exact contribution of recurrent UTIs to CKD progression in various pediatric populations is not yet well documented and constitutes an area for further research. Secondly, the effectiveness of interventional measures for dysfunctional elimination syndrome in reducing UTI recurrence and CKD risk requires further elucidation. There is



CKD, *chronic kidney disease*; **GFR**, *glomerular filtration rate*; **UTI**, *urinary tract infection*; **VUR**, *vesicoureteral reflux;* **ESKD**, end-stage kidney disease

Adaptive hyperfiltration: compensatory GFR elevation in the remaining normal nephrons.

Figure 2. Schematic diagram illustrating some predictors of chronic kidney disease risk in childhood urinary tract infection and the preventive nephrology strategies.

indeed no direct evidence linking such measures to reduced CKD risk in children. Nevertheless, interventions for dysfunctional elimination syndrome or bladder-bowel dysfunction—such as managing constipation with laxatives and diet, and maintaining adequate fluid intake—can indirectly reduce CKD risk by minimizing the frequency and severity of UTIs.[42] Optimizing bowel management is effective in reducing CKD risk associated with recurrent UTIs. More prospective studies are still required to establish the long-term kidney outcomes in affected children. Thirdly, some biomarkers appear promising for predicting kidney scarring after febrile UTIs. These include urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, urinary interleukin-6 (IL-6) and IL-8, and procalcitonin, which provide a non-invasive alternative to traditional imaging methods like ^{99m}Tc-DMSA scintigraphy.[43] Because there is no unanimity on the most predictive biomarkers, further research and high-quality clinical trials are essential to establish standardized thresholds and confirm their long-term predictive value for kidney scarring. Finally, given the knowledge gaps on the complex association between CKD and UTI in children, longitudinal studies are required to estimate the contribution of UTIs to CKD across CAKUT etiologies because about 50% of children with UTI have CAKUT.[44] On the other hand, CAKUT is a significant cause of childhood CKD, as many cases are characterized by recurrent UTIs, which may also result in adverse kidney outcomes.

CONCLUSION

The UTI may or may not be associated with significant kidney scarring that predisposes to future CKD risk. Kidney scars potentially complicate recurrent UTIs or acute pyelonephritis (febrile UTIs). Scarring appears accentuated in the presence of underlying urologic abnormalities such as VUR or CAKUT. Evidence-based data suggest that in the absence of these structural abnormalities or recurrent UTIs, CKD risk appears minimal. However, other reports not only contradict the practice of antibiotic prophylaxis in children with VUR which aimed to minimize incident UTI and prevent adverse kidney outcomes but also raise questions about the traditional VUR-UTI-kidney scar-CKD trajectory. The indirect and direct predictors of CKD risk include patient demographic factors (younger age and female sex),presence or duration of urologic abnormalities (e.g., VUR), high-grade VUR, bilateral or previous kidney scarring,andmicroalbuminuria. Some of these CKD risk predictors, and kidney scar-related complications such as hypertension, potentially accelerate CKD progression to late stages. The factors that potentially accelerate CKD progression should be targeted by kidney-protective strategies, such as managing structural risk factors like VUR, and screening for functional risk factors for CKD (e.g., proteinuria and hypertension), or risk markers (e.g., microalbuminuria), and applying pharmacologic or surgical interventions to mitigate these CKD risk factors.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.N.U.; Design – S.N.U.; Literature Search – S.N.U.; Writing Manuscript – S.N.U.; Critical Review – S.N.U.

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