

# Mini-review on pathogenesis and diagnosis of vesicoureteral reflux in children

## Abstract

Vesicoureteral reflux (VUR) represents nowadays a controversial issue regarding its diagnosis, screening and treatment for its potential renal damage is not clearly understood. We aim in this mini-review to study the pathogenesis of VUR mechanisms in order to understand its clinical presentation and then be able to evaluate evidence in its screening and diagnosis. Primary VUR is essentially related to short intravesical length of the ureter, while secondary reflux is more related to anatomic or neuro functional anomalies of the bladder. Prevalence of VUR is high in siblings and offspring of index patients making its genetic predisposition quite evident. Recommendations in evaluation of VUR in case of antenatal hydronephrosis or urinary tract infection (UTI) differ among experts and organizations with benefits and inconveniences to each attitude.

**Keywords:** vesicoureteral reflux, pediatrics, pathogenesis, diagnosis

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**Abbreviations:** VUR, vesico ureteral reflux; UTI, urinary tract infection; APN, acute pyelo nephritis; UVJ, uretero vesical junction; CND, common nephric duct; UGS, uro genital sinus; BOO, bladder outlet obstructions; PUV, posterior urethral valves; LUTD, lower urinary tract dysfunction; AUA, American urological association; RPD, renal pelvic diameter; CAKUT, congenital anomalies of the kidney and urinary tract; EAU, European association of urology; RBUS, renal bladder ultra sound; AAP, American academy of pediatrics; ESPU, European society for pediatric urology; ESPR, European society of pediatric radiology; DMSA, di mercapto succinic acid; NICE, national institutes for clinical excellence

## Introduction

VUR is a common clinical entity which represents the retrograde flow of urine from the bladder into the upper urinary tract. Although VUR is a natural finding in many animal species,<sup>1</sup> its presence in humans is considered a misadventure. VUR is estimated at 0.4% to 1.8% in asymptomatic children, almost 1% in the pediatric population.<sup>2</sup> In a large meta-analysis done by Sargent,<sup>3</sup> cystography performed in children for various indications showed VUR in 30% of cases with UTI and in 17% without UTI. Up to 70% of neonates less than one year of age with a history of UTI have VUR. However, the real correlation between VUR and UTI is still controversial.<sup>4</sup> The main problem dealing with VUR is its prognosis; is there really a link between acute pyelonephritis (APN), recurrent UTI, renal scarring, renal failure and the presence of VUR? The purpose of this mini-review is to analyze the pathogenesis of VUR, trying to understand its etiologies and then evaluate evidence in its screening and diagnosis.

## Pathogenesis

VUR can be divided into two categories: primary and secondary. I. Primary VUR is related to an incompetent ureterovesical junction (UVJ) with failure of its closure by bladder compression during filling. The ureter has an intravesical part: one intramural and one submucosal. At the level of the extravascular bladder hiatus, the three

muscle layers of the ureter separate. The intravesical part is formed only by a longitudinal muscle segment which migrates distally forming the Bell's muscle (superficial trigone) and medially to the contralateral ureteral orifice forming the intraureteric bar of Mercier. The adventitia of the distal ureter merges with a longitudinal muscle sheath, called the Waldeyer's sheath, which ends at the distal bladder neck forming the deep trigone. This sheath anchors the distal ureter to the hiatus.<sup>1</sup> The studies of Paquin revealed an approximately 5/1 ratio of intravesical length to ureteral diameter in non refluxing junctions.<sup>5</sup> Reflux occurs initially in a case of lower ratio. Abnormalities in UVJ constitution as Waldeyer's sheath weakness or extracellular matrix composition may lead to VUR.<sup>6</sup> Concerning the embryology of the UVJ, the Wolffian duct and the ureteral bud form the two arms of a Y with the distal end of the mesonephric duct, called the common nephric duct (CND), constituting the stem of the Y. According to recent studies<sup>7</sup> dealing with the ureteral bud theory of Mackie and Stephens, CND undergo apoptosis after its migration to the urogenital sinus (UGS) which later becomes the bladder. Then, the two arms of the Y enter the bladder separately: one as the vas deferens and the other as the ureter. When the ureteral bud reaches the UGS too soon, its implantation into the bladder is high and lateral with a short intravesical length, leading to VUR. Moreover, anomalies concerning ureteral budding may affect the interaction between bud epithelium and the metanephros, making renal anomalies such as hypoplasia, dysplasia or agenesis an associated finding with VUR. II. Secondary reflux results from anomaly affecting the integrity of the ureter or the functional dynamics of the bladder. As an example of a ureteral anomaly, dilated ureters with alteration of their musculature are seen in Prune-Belly syndrome with VUR in 75% of the cases.<sup>8</sup> Bladder outlet obstructions (BOO) in children with elevated voiding pressures are considered responsible for VUR. The most common cause of BOO in male pediatric population is posterior urethral valves (PUV) with VUR seen in up to 70% of the patients.<sup>9</sup> In females, ureterocele represents the first common cause of BOO. Neurofunctional problems of the bladder lead to secondary reflux. Neurogenic bladder in a case of spina bifida is a known risk for reflux. Careful examination of the

lower back is crucial, looking for signs of occult spinal dysraphism as gluteal cleft, hairy patch and sacral dimple.<sup>10</sup> In toilet trained children, lower urinary tract dysfunction (LUTD) such as dysfunctional voiding or dysfunctional elimination syndrome are associated with reflux and UTI.<sup>11</sup> Management of LUTD in children is not always associated with VUR resolution, showing a borderline incompetent UVJ with probable deterioration by high voiding pressures and UTI.

## Epidemiology

When VUR is detected antenatally, it is more frequent in boys than in girls. Furthermore, it tends to be of high grade, bilateral and with higher chances of spontaneous resolution. In older children, girls are more likely to have reflux than boys.<sup>12</sup> In case of antenatal hydronephrosis defined in the systematic reviews conducted by the American Urological Association (AUA) as a renal pelvic diameter (RPD) superior to 4mm in the second trimester and 7mm in the third trimester, the prevalence of VUR is about 16%.<sup>13</sup> This prevalence reaches 38% in the presence of severe hydronephrosis or urological anomalies such as renal cysts or renal agenesis.<sup>14</sup> It is important to mention that the degree of RPD is not in a correlation with the presence of VUR as for other congenital anomalies of the kidney and urinary tract (CAKUT).<sup>15</sup> Ethnicity is considered an important risk factor for VUR with female of African descent 10 times at lower risk than White and Caucasian. At age of 10years, risk is the same independently to ethnicity, probably related to a delay of maturation of the UVJ in White and Caucasian children.<sup>16</sup>

## Genetics

Genetic predisposition is quite clear for the prevalence of VUR is 100% in identical twin siblings.<sup>17</sup> Systematic review shows rates of 27.5% for siblings and 35.7% for offspring of an index patient.<sup>13</sup> In animals, many genes responsible for VUR have been detected, with an autosomal dominant mode of transmission: PAX2, RET, Uroplakine III, AGTR2, RET... However, no specific gene has been shown producing VUR in humans, making probably its appearance a more complex polygenetic mechanism.<sup>18</sup> Viewing this high risk of VUR, the European Association of Urology (EAU) and the AUA recommend screening asymptomatic siblings and offspring by renal bladder ultrasound (RBUS) in order to prevent UTI and renal damage if VUR is diagnosed early.<sup>13,19</sup> In fact, there are little high-level data on screening asymptomatic siblings and offspring of VUR index patients. Assessment must be based on family history, compliance with follow-up, clinical exam (e.g. blood pressure), presence of UTI and LUTD.

## Diagnosis

Guidelines concerning initial evaluation of VUR differ among organizations. Controversies exist for the real clinical course of VUR is not well known. When hydronephrosis is detected antenatally, evaluation for VUR postnatally is done by RBUS. Voiding cystourethrogram is an initial test for some experts,<sup>20</sup> while others reserve it for cases of associated anomalies on prenatal ultrasound, persistent ureteral dilatation or hydronephrosis on postnatal ultrasound, presence of a family history of VUR or the development of UTI during observation.<sup>21</sup> The main problem is that postnatal ultrasound is not sensitive screening tests that will miss VUR cases, even those with high grade.<sup>22</sup> On the other hand, VCUG is an invasive procedure with need of urethral catheterization, radiation exposure and 1% risk of UTI. The American Academy of Pediatrics (AAP) has changed its recommendation of 1999 when RBUS and VCUG were indicated after a first episode of febrile UTI for the diagnosis of VUR.

Today, VCUG is to be done in case of recurrent UTI, hydronephrosis, ureteral dilatation or the presence of a renal scar.<sup>23</sup> This change is based on the fact that two studies of compliance with the old guidelines showed that only 39.5% to 61% of children had VCUG after their first UTI.<sup>24,25</sup> A new prospective study highlights the fact that only 39% of patients had VUR after their first febrile UTI with 96% of them with low grade reflux, considered a low risk for further renal damage.<sup>26</sup> The European Society for Pediatric Urology (ESPU) and the EAU recommend for VCUG in addition to RBUS, considering that early diagnosis may prevent bad prognosis of VUR.<sup>19</sup> However, this remains controversial. The European Society of Paediatric Radiology (ESPR) focused on determining renal injuries as APN, renal scar or dysplasia, considering that only clinically relevant VUR with potential to cause renal damage is worthy of uncovering.<sup>27</sup> This is called the top-down approach with a dimercaptosuccinic acid (DMSA) renal scan performed at initial evaluation. VCUG is reserved only in case of abnormal DMSA scan. Top-down approach is not without limitations; a recent meta-analysis has shown that DMSA scan poorly detects high grade VUR, with sensitivity and specificity of only 79% and 53% respectively.<sup>28</sup> National Institutes for Clinical Excellence (NICE) guidelines note that extensive evaluation of a child after his first episode of UTI is inappropriate. VCUG is limited to children less than 6months of age with recurrent or atypical UTI and children between 6months and 3years with recurrent or atypical UTI and hydroureter, hydronephrosis, family history of VUR, non *E. Coli* infection or poor urine flow.<sup>29</sup> Despite the fact that high predictive values of NICE guidelines were noted in one study,<sup>30</sup> others showed serious problems. Between nine children with grade III-V VUR, five would have not been detected by the NICE guidelines; four of them were in need for surgery.<sup>31</sup>

## Conclusion

The present mini-review explains pathogenesis of VUR and emphasizes controversy and different guidelines regarding VUR imaging, screening and initial diagnosis. Although many data can be studied for arguments, no consensus about whether a kidney- or bladder- central approach is better for first evaluation of VUR. Future research should target on improving tools to identify children who are at risk of VUR-related renal damage.

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## Conflict of interest

The author declares no conflict of interest.

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