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Vesicoureteral reflux in infants: what do we know about the gender prevalence by age?

N. CAPOZZA[1], C. GULIA[2], Z. HEIDARI BATENI[3], A. ZANGARI[4], S. GIGLI[5], V. BRIGANTI[4], S. TURSINI[4], C.J. KOH[3], M. GAFFI[4], S. BALDASSARRA[2], F. SIGNORE[6], A. PORRELLO[7], R. PIERGENTILI[8]

[1]Urologic Surgery Unit, Pediatric Hospital "Bambino Gesù", Rome, Italy
[2]Department of Gynecology, Obstetrics and Urology, Policlinico Umberto I Hospital, Sapienza University, Rome, Italy
[3]Texas Children's Hospital Pavilion for Women. Ob/Gyn Department, Fetal Surgery Center, Baylor College of Medicine, The Hospital for Sick Children, Houston, Texas, USA
[4]Pediatric Surgery and Urology Unit, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy
[5]Department of Radiology, Anatomo-pathology and Oncology, Policlinico Umberto I Hospital, Sapienza University, Rome, Italy
[6]Department of Obstetrics and Gynecology, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy
[7]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[8]Institute of Molecular Biology and Pathology, Italian National Research Council (CNR-IBPM), Rome, Italy

Nicola Capozza and *Caterina Gulia* contributed equally to the work

Abstract. – OBJECTIVE: Vesicoureteral reflux (VUR) affects up to 1% of Caucasian children. Primary VUR is characterized by failure of the ureterovesicular junction to prevent urine from traveling in a retrograde fashion from the bladder to the ureters and the kidneys. Several reports in the literature describe the prevalence of this condition in pediatric patients; overall, VUR affects more males during infancy and with higher grades. However, a thorough consideration of these articles reveals important contradictions regarding the prevalence by gender and age. We analyzed those contradictions and suggested a possible explanation based on our single center experience with this patient group. In particular, for the age interval 0-2 years: we have found that (1) VUR mostly affects boys; (2) the male/female ratio steadily declines over time; (3) the unequal prevalence between males and females essentially disappears when children reach the age of two years.

CONCLUSIONS: The natural history of VUR in infant boys differs from that of infant girls, and therefore requires a gender-specific approach. Available data support the need to redefine the categorization and clinical guidelines for this disease.

Key Words:
Epidemiology, Gender medicine, Incidence, Prevalence, Genetics of vesicoureteral reflux.

Introduction

Vesicoureteral reflux (VUR) (OMIM entry: 193000) is the retrograde reflux of urine from the bladder into the ureter and, in some instances, to the kidneys[1].

Primary VUR is caused by congenital anomalies of the ureterovesicular junction leading to an incompetent valve mechanism. This condition is dependent on the insufficient submucosal length of the ureter inside the bladder walls that in turn cannot exert their function, i.e., constriction of the ureter to control the urine flux. The "sufficient" length is not a fixed parameter and rather depends on the ratio between the submucosal tract length and the diameter of the ureter itself. Briefly, the ureter enters the bladder wall with an angle less than 90 degrees, and the smaller the angle, the longer is the tract of ureter embedded inside the bladder wall before it exits into the bladder lumen. The submucosal ureter length is considered "adequate" when it allows a proper valve mechanism[2].

On the other hand, secondary VUR is an acquired condition that is a consequence of high pressure inside the bladder, despite the presence of a functional valve mechanism. This type of

Corresponding Author: Alessandro Porrello, Ph.D; e-mail: aporrelloresearch@yahoo.com
Roberto Piergentili, Ph.D; e-mail: roberto.piergentili@uniroma1.it

VUR may be caused by anatomical or functional obstructions[3,4], such as posterior urethral valves, urethral or meatal stenosis (anatomical blockage), bladder instability, neurogenic and non-neurogenic bladder[5].

VUR is frequently associated with two other conditions: urinary tract infections (UTI)[6] and renal scarring that, in severe cases, can lead to hypertension and renal failure[7]. In particular, UTI leads to reflux due to an increased inflammation-related intra-bladder pressure. Children with UTI can have VUR, and the contemporary presence of both conditions often correlates with renal damage, with a direct relationship between the number of UTI episodes and renal scar formation[8]. All treatments preventing UTI (such as circumcision in males) have a positive effect in preventing renal damage, especially at younger ages[9]. However, VUR *per se* and without concomitant UTI does not cause renal damage[10], and the rate of spontaneous resolution of high-grade VUR is independent of the presence of intrarenal reflux[11]. Spontaneous resolution is possible, and an inverse relation between grade and resolution has been described[12]; the patient's gender is another important variable (female patients are more prone to non-resolution)[13].

The severity of VUR is measured using an ordinal scale of five degrees, as shown in Table I (based on the work of Greenbaum and Mesrobian)[3].

VUR Incidence and Prevalence

Data about VUR incidence and prevalence are uncertain and only estimations may be drawn. This is mainly caused by the absence, in most cases, of specific symptoms, especially when this condition is not associated with UTI; this brings to undiagnosed patients, for whom the discovery of this alteration is usually accidental. To date, a prevalence between 0.4% and 1.8% is estimated for children without other concomitant conditions[14]. This percentage rises to ~16% among infants showing prenatal hydronephrosis[15], and further increases in the presence of familiarity, indicating a genetic predisposition in some cases[16,17]. However, the spontaneous resolution of VUR in children, especially males[18], might determine an underestimation of its prevalence among relatives. VUR incidence is also quite high (7-17%) in children affected by end-stage renal disease[19,20].

Several groups have searched for a genetic cause of VUR. To date, some genes have been specifically linked to this condition[21] and also the genetic predisposition to UTI is currently under investigation[22]. Some Authors[23-25] have described an incidence of 27% in siblings of patients with VUR and a 66% rate for those whose parents had VUR during childhood[26], thus revealing a familial aggregation. Despite these reports, there is no agreement yet among experts about the exact mode of inheritance. Indeed, VUR has been described either as an autosomal dominant trait with incomplete penetrance[27,28], or an autosomal recessive trait[29], or an X-linked condition[30] or even a polygenic disease[31]; to date, at least nine chromosomal loci have been related to VUR, and some genes have been identified[1].

Although UTIs are more frequent in girls because of their anatomy, VUR affects more boys, with a higher grade and at a younger age, but also with better chances of spontaneous resolution[32-35]. Altogether, the literature about VUR is large (VUR was first described by Pozzi in 1893)[36] and complex, because of contradictory management recommendations and unclear data about the gender-related prevalence. This last fact is, at least partially, due to diagnostic issues: girls are usually diagnosed for VUR later than boys. However, data retrieved from the literature seem to suggest a more complex scenario. Godley and Ransley[2] performed an extensive analysis and compared data from 15

Table I. VUR grading, corresponding ureter size status, and involved organs.

Grading	Ureter size status	Involved organs
Grade I	Non-dilated	Ureter only
Grade II	Non-dilated	Renal pelvis and calyces
Grade III	Mildly dilated	Mild dilation of the pelvicalyceal system, minimal blunting of the fornices
Grade IV	Mild dilatation associated with moderate tortuosity	Blunt fornices but preserved papillary impressions
Grade V	Gross dilatation and tortuosity	Dilated pelvis and calyces, loss of both fornices and papillary impressions

cohorts of patients of different sex and age. They grouped the reports according to patients' age, creating four sets: (1) infants (< 1 year, 5 reports published between 1970 and 2006), (2) 0-2 years (two reports, in 1999 and 2006), (3) 0-15 years (7 reports, published from 1975 to 2006) and (4) adults (> 15 years; 1 report in 1990). The first evident conclusion we made is the non-obvious subdivision of age ranges, which shows remarkable overlaps for the youngest ages. This happens because most reports are not consistent regarding two issues: (1) who is defined as an infant and who is not (first two sets), and (2) the fact that it is common to pool results from distinct studies, despite ample age variations, to perform a more robust statistical analysis [see the aforementioned point (3)]. However, the most striking contradiction about the data retrieved by Godley and Ransley[2] is the large fluctuation in the males/females (M:F) ratio, especially at the lowest ages[2]. In infants aged 0-12 months, this ratio ranges from 1.6 (i.e., 1.6:1) to roughly 0.59 (i.e., 1:1.7); in the interval 0-2 years, it goes from 1 (1:1) to approximately 0.33 (1:3); and in the interval 0-15 years it is between 0.5 (1:2) and 0.25 (1:4). Notably, in adults (i.e., > 15 years, based on one report) it drops to 0.20 (1:5). Clearly, the data based on the youngest ages are contradictory, despite the general conclusions previously described, which are also shared by Godley and Ransley[2] (infant boys and non-infant girls are the most affected patients). Indeed, there seems to be a "stabilization" of these ratios with increasing ages, towards a significantly higher prevalence in girls. This tendency in the information collection, i.e., pooling together inhomogeneous data, is also common in recent reports[35,37]; interestingly, the VUR numerical trends for boys and girls reported by Godley and Ransley[2] are in agreement with the most recent data[37]. Collectively, these data strongly suggest that an ample age fork in the available literature somehow "masks" the sex-related VUR prevalence in the youngest patients, especially males.

A More Accurate Age Subdivision Reveals New Age- and Sex-related VUR Features in Infants

We searched for an answer to two main questions: (1) why are males more affected than females at younger ages, and with a higher VUR degree, yet they show a higher proportion of spontaneous healing? (2) Why are females more affected at older ages, and have a lower probability of spontaneous healing, despite their generally milder condition? To obtain additional clues about the possible mechanisms responsible for VUR formation, we reviewed the records of the Operative Unit of the Department of Urology of the Children Hospital "Bambino Gesù" of Rome, Italy, which were collected between January 2007 and December 2010. These data have a peculiarity that is missing in all other published research on this subject: for each patient, the age is defined as 'days from birth to the time of diagnosis'. Therefore, it is possible to group the children using much smaller age ranges than previously. In this data set, a total of 464 cases of primary VUR were diagnosed after the first febrile UTI in children aged 2 years or less. These data are reported in Table II, in which children were split by sex and age in time intervals of 90 days for ages > 180 days, and pooled only before the 180th day, because of the limited number of patients available in this early time window.

There is a clear difference between the number of boys (295) and girls (163), in the total population of pediatric patients that were treated in this hospital, in the analyzed time frame of children's ages (i.e., two years). Additionally, the general M:F ratio observed for them (M:F = 295:169≈1.75) is consistent with the literature[2].

It is common practice that males are monitored for this condition after the first febrile UTI; instead, females are screened after the second or even third episode, due to their anatomical predisposition to infections. Consequently, in other studies girls were diagnosed for VUR later than boys, thus introducing a time bias that possibly influences the VUR grade at the time of diagnosis. On the contrary, the patients of our dataset were all diagnosed after the first febrile UTI, and this approach eliminated this potential confounding factor (that is inadvertently overlooked by some Authors). An analysis of the data focused on children's age (each interval spanning three months, except the first (180 days) and last (100 days) ones) allowed us to determine how this condition affects the M:F ratio during the first two years of life. From Table II and Figure 1 it is easy to highlight that (1) male infants with VUR are much more numerous than coetaneous females, in agreement with the literature; (2) males are more affected than females at younger ages, as reported in the papers cited by Godley and Ransley[2]; (3) the M:F ratio decreases when the patients' age

Table II. Screening for VUR at the "Bambino Gesù" Hospital during the years 2007-2010.

Age (days) year/sex		≤ 180	181-270	271-360	361-450	451-540	541-630	631-730	Total	M:F Ratio by year
2007	M	2	9	12	10	13	14	7	67	2.0
	F	1	4	6	5	10	4	3	33	
2008	M	2	14	10	12	11	7	10	66	1.7
	F	1	6	10	4	4	6	9	40	
2009	M	9	16	19	11	3	6	6	70	1.9
	F	0	6	5	9	9	4	3	36	
2010	M	4	23	19	18	11	12	5	92	1.5
	F	3	11	12	7	6	10	11	60	
Total	Total M	17	62	60	51	38	39	28	295	1.7
	Total F	5	27	33	25	29	24	26	169	
M:F ratio by age		3.4	2.3	1.8	2.0	1.3	1.6	1.1		

Data are organized by age (expressed in days) for males (M) and females (F). Age intervals last 90 days, except the first interval (column 1, showing cumulative data for infants of less than 180 days of age) and the last interval (column 7, spanning 100 days, in order to reach the age of two years, i.e., 730 days). The M:F ratios are calculated both on the totals for each year (last column) and on the totals for each age interval in the whole time frame considered (last row), rounded to the one decimal place. Note that while the M:F ratio by year is fairly stable over time, the M:F ratio by age shows a decrease when the children's age increases. The diagnosis was assessed using retrograde cystography; results were evaluated both by a radiologist and a pediatric urologist. All patients were assigned to grades II-V and subsequently treated according to the available protocols. Grade I patients were excluded from this table unless, during the follow-up checks, their grade increased; we made this choice because grade I patients are frequently subject to spontaneous resolution[32-34].

increases. This third point was only partially suggested by the works discussed by Godley and Ransley[2]. A sharp distinction between our data set and others is that, unexpectedly, while for 0-6 months old infants the M:F ratio is roughly 3, for 21-24 months old children this value approximately drops to 1 (Table II). Therefore, our records show that the M:F ratio drift is essentially due to a change in the number of boys, since the number of girls is almost constant in the 6-24 months age frame (Table II and Figure 1). These data illustrate that the VUR prevalence in males depends on the patient's age, while in females is largely independent of this variable. Remarkably, analyzing the data of the Children Hospital "Bambino Gesù" (Rome, Italy) without any possible bias created by the use of arbitrary time windows confirms these observations. Indeed, the probability density functions (pdf) of the time of diagnosis for males and females are both skewed to the left (i.e., they have positive skewness). However, (1) the boys' skewness is 0.2876 and the girls' skewness is roughly one-third of this value (0.1034) and (2) the ratio (97.5 percentile – median) / (median – 2.5 percentile) is considerably greater for boys (1.5552) than for girls (1.1146)[38]. Overall, the pdf of girls is much more "flat" than the pdf of boys, thus confirming the existence of an early age peak for the latter group of patients.

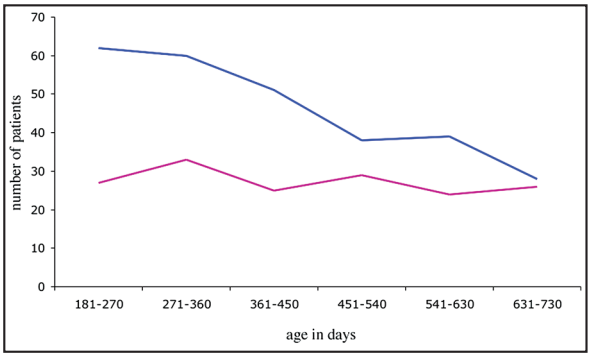

Figure 1. Total number of boys (*blue, upper line*) and girls (*pink, lower line*) affected by VUR, with ages between 6 and 24 months. This graph is based on the cumulative data of these patients, which are reported in Table II, row 5.

Interestingly, the data from "Bambino Gesù" Hospital about infant boys match the data from the literature[39], since the prevalence of affected males in newborns is much higher than that of females. An analysis of published articles also reveals that males tend to have higher grades of VUR at younger ages, but their condition is more prone to spontaneous resolution[12,32-34]. Some Authors conjecture that this natural healing might be secondary to an increase in the intramural length of the ureter caused by normal growth[2,3]. Thus, we hypothesize that the VUR affecting males and females are different medical conditions, because

of their different epidemiology (distinct age-dependent prevalence in the two genders, Figure 1) as well as the possibility of spontaneous healing in boys (data from the literature). As a consequence, during growth the M:F ratio declines (Figure 1) and, notably, several Authors[2,20,39,40] have described that, at some point, girls become more affected by VUR than boys.

We explain the – now, only apparent – contradiction between a higher VUR prevalence in either sex, especially below the age of two, by introducing the "age range" as a critical variable. The exact causes of the "female" VUR are unknown, and also it is unclear if their particular onset of VUR might actually affect both sexes. However, since VUR and UTI are related conditions, the simpler and shorter – and, consequently, more prone to infections – female urinary apparatus may be involved. It is intriguing to hypothesize that VUR in girls is a consequence of their anatomy and that the primary cause of reflux for them is connected with UTI occurrence, at least in a significant number of cases. Indeed, a recent report shows that febrile UTI incidence is independent of VUR presence in girls aged 0-24 months[41]. If this were true, VUR in girls would be, in many cases, the effect of environmental factors. Some Authors[15,16,22] have already hypothesized that certain cases of VUR may be the consequence of gene-environment interactions. However, we believe that there is also a male-specific VUR. In 1997, Yeung et al[40] showed that a mild form of reflux affects females more than males and that this VUR is not connected with kidney abnormalities. Instead, severe reflux is frequently associated with kidney damage, is probably of fetal origin, and is almost exclusively a male disorder. This suggests that, for some reason(s), the urogenital tract of males during development is more prone to VUR than that of females. It is known that prenatal reflux is more frequent in males[40] and that refluxes diagnosed before the age of one year are more prone to spontaneous resolution[40,42]. Also, the male apparatus is more complex and its maturation ends at birth[43], similarly to what happens in other primates, where VUR spontaneously heals in most cases and both sexes within 2-3 years from birth. This outcome implies "that the attainment of full competence by the ureterovesical junction is a matter of maturation rather than of growth"[44]. Thus, it is possible that in some cases (for example, due to minor genetic alterations or because of slightly untimely physiological signals caused by environmental factors, which produce low impact modifications)[45], the male urogenital tract maturation may be delayed after the birth to some extent. This is indeed true for the intramural length of the male ureter, which increases in size up to 10-12 years old[2,3]. Nevertheless, since no major alterations are involved in the biochemical pathways, VUR would spontaneously resolve, in most subjects, before birth. It has been suggested an inverse relationship between VUR spontaneous resolution on the one side and duration of the VUR[46] and patients' age[47] on the other side. Therefore, in most male infants VUR may be considered somehow "physiological", at least under certain circumstances[15]. This observation would explain the high rate of spontaneous healing in males, compared to females. Instead, in all cases in which the reflux persists in boys, or is of high grade, VUR has to be considered a "non-physiological" condition and should be treated accordingly[4,48].

How Many VURs Are There?

In a recent review[48], the Authors wrote in their conclusions: "The present literature is marked by controversy and divergent guidelines regarding VUR imaging, screening, and treatment, although there are multiple areas of consensus." Indeed, there are several studies that either (1) recommend treatment with antibiotics, or (2) suggest their ineffectiveness to prevent UTI in VUR-affected children, or (3) discuss the use of antibiotics *v*s. surgery[19,20,48-50]. Even VUR imaging[51] and UTI diagnostics[52] are debated topics in general VUR management[53-55]. We believe that these contradictions and the lack of homogeneous treatment protocols occur because there are several types of VUR, each needing different guidelines for clinical management.

It is well known from the literature that VUR may be either primary or secondary. The latter is due to functional or anatomical obstructions; consequently, the removal of the obstacle generally leads to healing. Instead, primary VUR is a more complex condition. Primary VUR may be associated with other anomalies (syndromes) affecting mainly the kidney(s) development. Overall, despite its name, primary VUR probably is not the primary event for these patients. Instead, in primary VUR a genetic alteration likely leads to embryonic development abnormalities that, eventually, cause several defective phenotypes including, but not limited to, VUR. Notably, there are also genetic anomalies that interfere with the

formation of a normal vesicoureteral junction without affecting any other part of the urogenital tract (we define these as non-syndromic VUR); indeed, in most cases, children affected by VUR have normal kidneys[14]. In a research based on a mouse model the Authors[56] were able to genetically separate VUR and small kidney phenotypes. They also demonstrated that the implicated gene(s), which map on autosomes, are involved in a delay of the urinary tract development. This last finding is noteworthy, since it suggests a strong difference between syndromic and non-syndromic VUR. Both types are presumably of genetic origin, but the former may be a "failure" in some early step of the urogenital tract development, while the latter could merely be a "delay" in a (likely) later step of the same developmental pathway. This lag is possibly mediated by a gene/environment interaction that perturbs the normal urogenital tract maturation to some extent. In humans, different steps of this process are controlled by different sets of genes[57], and several genetic alterations may induce VUR, either alone or together with other urogenital conditions. This would explain the genetic heterogeneity of the VUR phenotype, involving mutations in different genes, located on different chromosomes. Some of these mutations are dominant (but occasionally show incomplete or age-dependent penetrance) while others are recessive or X-linked (see the "VUR incidence and prevalence" section).

Thus, the abovementioned results from the mouse model of Murawski et al[56] and a comparison of the available literature with our data suggest a new VUR classification, based on gender, syndromic nature and etiology (Figure 2). Putting together our clinical knowledge and what is known from the literature, we propose a flowchart that can be used by physicians that want to effectively deal with this condition keeping into account what has been discussed in this review about the gender and age variables (Figure 3).

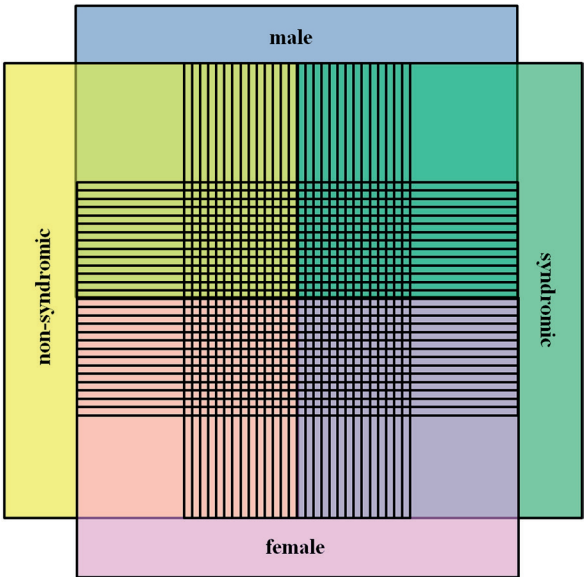

Figure 2. Etiology and features of VUR represented by a non-Venn diagram. VUR may affect both males and females, which are shown at the top and bottom halves (blue and pink color, respectively) without mutual overlap. Also, VUR may be the only condition (non-syndromic) or one of the multiple phenotypes of a complex, multi-organ disease (syndromic). These two possibilities are shown at the left and right halves of the diagram (yellow and green color, respectively) and do not overlap each other, but overlap both sexes. Finally, the causes of VUR may either be the (mis)action of specific genes, or environmental factors, or gene/environment interactions. Horizontal and vertical lines represent environmental and genetic factors, respectively. This classification subdivides the diagram into 16 rectangles. We distinguish the following cases: (1) male, non-syndromic, unknown etiology (pale green); (2) male, non-syndromic, VUR induced by genetic factors only (pale green with vertical lines); (3) male, syndromic, VUR induced by genetic factors only (dark green with vertical lines); (4) male, syndromic, unknown etiology (dark green, top right); (5) male, non-syndromic, VUR induced by the environment only (pale green with horizontal lines); (6) male, non-syndromic, VUR induced by genetic and environmental factors (pale green with squares); (7) male, syndromic, VUR induced by genetic and environmental factors (dark green with squares); (8) male, syndromic, induced by the environment only (dark green with horizontal lines). In the bottom half of the figure, there are 8 additional cases that are homologous to cases 1-8, but concern females instead of males. This diagram intends to represent only the identities of these 16 (8 + 8) cases/groups of patients (i.e., the sizes of the 16 sectors of this diagram are not quantitative with respect to the entire population of patients).

Conclusions

In their well-known article on VUR, Kelly and co-workers state: "The former conclusion that VUR is a homogeneous disorder is no longer tenable; it is clearly heterogeneous"[60]. Our data, combined with those previously published, strongly suggest that VUR is genetically heterogeneous and is not just one condition, but rather an ensemble of different cases, each characterized by different causes (Figure 2). For this reason, we evaluated a spectrum of clinical treatment plans that accounts for this diversity (Figure 3). In addition, the VUR classification may require modifications dealing with possible inter-

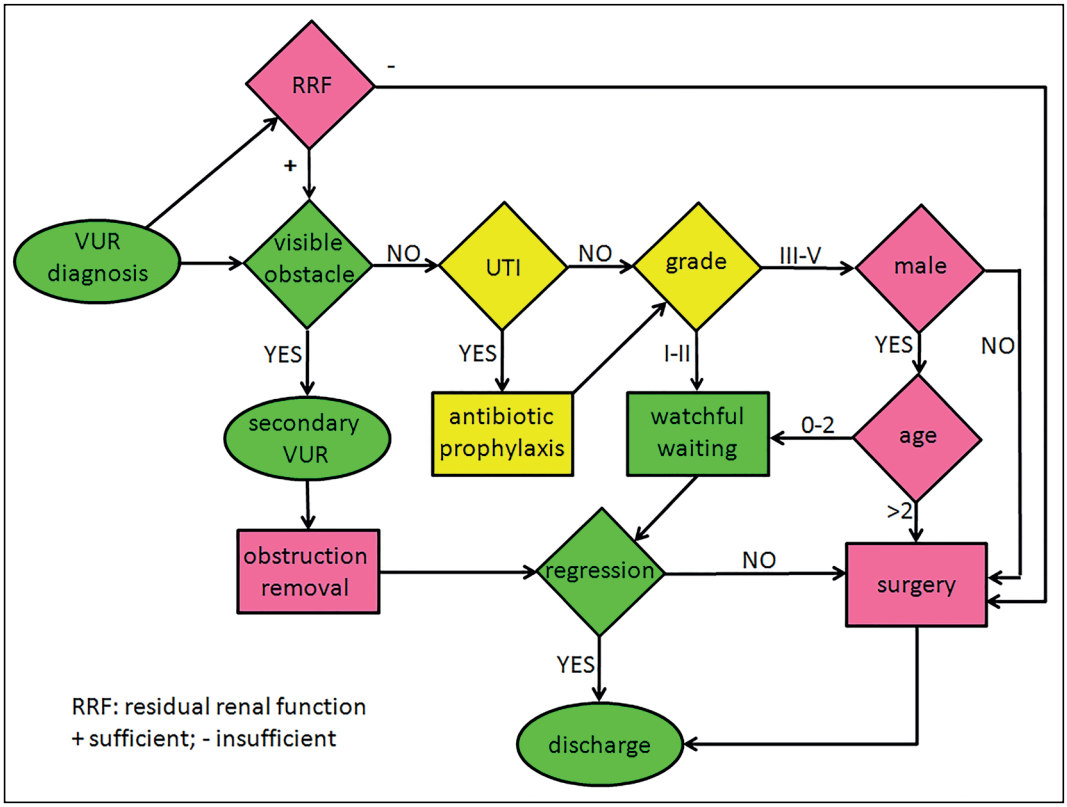

Figure 3. A simplified flowchart for the clinical management of VUR; this graph is partially based on the existing literature on this subject and includes, as critical nodes, the two variables (sex and age) that are evaluated in this review. This chart is intended solely for showing a possible sequence of steps taken by physicians and is not meant to be comprehensive or directly applied to all patients. Some of the steps that we describe as sequential may also happen at the same time or be chronologically swapped. For example, usually, the diagnosis of primary/secondary VUR, the assessment of renal damage and the evaluation of (febrile) UTI are done at the same time. Starting from the utmost left, once VUR is diagnosed, it is crucial to evaluate the residual renal function (RRF) and the presence of any visible obstacle causing the reflux; either of these two conditions may induce the physician to choose an invasive approach, such as surgery, to treat the patient. Moreover, the presence of UTI should be monitored along all the steps of this flowchart, since UTI may occur/recur after the VUR diagnosis, and antibiotic prophylaxis should be performed before sending the patient to the operating room. We suggest "watchful waiting" as a valid option in two cases: (1) in low VUR grades for any sex and age (as suggested by our knowledge and shared clinical experience) or (2) in infant males, especially with grades III and IV (based on the present report). Indeed, the spontaneous resolution of higher VUR grades in infant males or in prenatal cases has been described in the literature[58,59]. However, the final decision to apply this approach to infant males with a grade V and without renal damage and UTI is necessarily left to the judgment of the pediatric urologist, on a case-by-case basis and according to his/her experience and knowledge of this matter. The red color indicates nodes (RRF, obstruction removal, male, age, surgery) that are considered crucial, for our report and/or from a general medical standpoint; the green represents the least invasive actions/events/clinical variables (VUR diagnosis, visible obstacle, watchful waiting, regression, discharge); the yellow marks important actions/events/clinical variables and mildly invasive approaches (remaining nodes). Ovals mean start, end, or key intermediate step; diamonds are medical decisions/choices; rectangles are clinical actions.

actions between the genetic background and the gender/age variables. We encourage investigators to publish their genetic analyses of VUR using/taking into account younger ages and narrower age subdivisions, in order to (1) confirm that this condition affects patients differently according to their gender and (2) create a link between genetic makeup and age and gender of these subjects. The potential generalization of these assessments would identify VUR as a topic of personalized medicine and, even more importantly, help redefine VUR treatment guidelines accordingly.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) OMIM web site; https://omim.org/entry/193000. Accessed August 4, 2016.
2) Godley ML, Ransley PG. Vesicoureteral reflux: pathophysiology and experimental studies. In: Gearhart, Rink, Mouriquand eds., Pediatric Urology, 2nd edn. 2010; pp. 283-300.
3) Greenbaum LA, Mesrobian HG. Vesicoureteral reflux. Pediatr Clin North Am 2006; 53: 413-427.
4) Tekgul S, Riedmiller H, Hoebeke P, KoÐvara R, Nijman RJ, Radmayr C, Stein R, Dogan HS; European Association of Urology. EAU guidelines on vesicoureteral reflux in children. Eur Urol 2012; 62: 534-542.
5) Cooper CS. Diagnosis and management of vesicoureteral reflux in children. Nat Rev Urol 2009; 6: 481-489.
6) Blumenthal I. Vesicoureteric reflux and urinary tract infection in children. Postgrad Med J 2006; 82: 31-35.
7) Leonardo CR, Filgueiras MF, Vasconcelos MM, Vasconcelos R, Marino VP, Pires C, Pereira AC, Reis F, Oliveira EA, Lima EM. Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. Pediatr Nephrol 2007; 22: 1891-1896.
8) Swerkersson S, Jodal U, Sixt R, Stokland E, Hansson S. Relationship among vesicoureteral reflux, urinary tract infection and renal damage in children. J Urol 2007; 178: 647-651.
9) Evans K, Asimakadou M, Nwankwo O, Desai D, Cherian A, Mushtaq I, Cuckow P, Duffy P, Smeulders N. What is the risk of urinary tract infection in children with antenatally presenting dilating vesico-ureteric reflux? J Pediatr Urol 2015; 11: 93.e1-6.
10) Craig JC, Irwig LM, Knight JF, Roy LP. Does treatment of vesicoureteric reflux in childhood prevent end-stage renal disease attributable to reflux nephropathy? Pediatrics 2000; 105: 1236-1241.
11) Fukui S, Watanabe M, Yoshino K. Intrarenal reflux in primary vesicoureteral reflux. Int J Urol 2013; 20: 631-636.
12) Edwards D, Normand IC, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. Br Med J 1977; 2: 285-288.
13) Kirsch AJ, Arlen AM, Leong T, Merriman LS, Herrel LA, Scherz HC, Smith EA, Srinivasan AK. Vesicoureteral reflux index (VURx): a novel tool to predict primary reflux improvement and resolution in children less than 2 years of age. J Pediatr Urol 2014; 10: 1249-1254.
14) Sargent MA. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol 2000; 30: 587-593.
15) Williams G, Fletcher JT, Alexander SI, Craig JC. Vesicoureteral reflux. J Am Soc Nephrol 2008; 19: 847-862.
16) Conte ML, Bertoli-Avella AM, de Graaf BM, Punzo F, Lama G, La Manna A, Grassia C, Rambaldi PF, Oostra BA, Perrotta S. A genome search for primary vesicoureteral reflux shows further evidence for genetic heterogeneity. Pediatr Nephrol 2008; 23: 587-595.
17) van Eerde AM, Duran K, van Riel E, de Kovel CG, Koeleman BP, Knoers NV, Renkema KY, van der Horst HJ, Bökenkamp A, van Hagen JM, van den Berg LH, Wolffenbuttel KP, van den Hoek J, Feitz WF, de Jong TP, Giltay JC, Wijmenga C. Genes in the ureteric budding pathway: association study on vesico-ureteral reflux patients. PLoS One 2012; 7: e31327.
18) Farhat W, McLorie G, Geary D, Capolicchio G, Bägli D, Merguerian P, Khoury A. The natural history of neonatal vesicoureteral reflux associated with antenatal hydronephrosis. J Urol 2000; 164: 1057-1060.
19) Cooper CS, Chung BI, Kirsch AJ, Canning DA, Snyder HM 3rd. The outcome of stopping prophylactic antibiotics in older children with vesicoureteral reflux. J Urol 2000; 163: 269-272.
20) Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006; 117: 626-632.
21) Nino F, Ilari M, Noviello C, Santoro L, Rätsch IM, Martino A, Cobellis G. Genetics of vesicoureteral reflux. Curr Genomics 2016; 17: 70-79.
22) Hains DS, Schwaderer AL. Genetic variations in vesicoureteral reflux sequelae. Pathogens 2016; 5: pii:E14.
23) Parekh DJ, Pope JCT, Adams MC, Brock JW 3rd. Outcome of sibling vesicoureteral reflux. J Urol 2002; 167: 283-284.
24) Pirker ME, Colhoun E, Puri P. Renal scarring in familial vesicoureteral reflux: is prevention possible? J Urol 2006; 176: 1842-1846.
25) Giannotti G, Menezes M, Hunziker M, Puri P. Sibling vesicoureteral reflux in twins. Pediatr Surg Int 2011; 27: 513-515.
26) Noe HN, Wyatt RJ, Peeden JN Jr, Rivas ML. The transmission of vesicoureteral reflux from parent to child. J Urol 1992; 148: 1869-1871.
27) Sanna-Cherchi S, Reese A, Hensle T, Caridi G, Izzi C, Kim YY, Konka A, Murer L, Scolari F, Ravazzolo R, Ghiggeri GM, Gharavi AG. Familial vesicoureteral reflux: testing replication of linkage in seven new multigeneration kindreds. J Am Soc Nephrol 2005; 16: 1781-1787.
28) van Eerde AM, Koeleman BP, van de Kamp JM, de Jong TP, Wijmenga C, Giltay JC. Linkage study of 14 candidate genes and loci in four large Dutch families with vesico-ureteral reflux. Pediatr Nephrol 2007; 22: 1129-1133.
29) Weng PL, Sanna-Cherchi S, Hensle T, Shapiro E, Werzberger A, Caridi G, Izzi C, Konka A, Reese AC, Cheng R, Werzberger S, Schlussel RN, Burk RD, Lee JH, Ravazzolo R, Scolari F, Ghiggeri GM, Glassberg K, Gharavi AG. A recessive gene for primary vesicoureteral reflux maps to chromosome 12p11-q13. J Am Soc Nephrol 2009; 20: 1633-1640.

30) Naseri M, Ghiggeri GM, Caridi G, Abbaszadegan MR. Five cases of severe vesico-ureteric reflux in a family with an X-linked compatible trait. Pediatr Nephrol 2010; 25: 349-352.

31) de Vargas A, Evans K, Ransley P, Rosenberg AR, Rothwell D, Sherwood T, Williams DI, Barratt TM, Carter CO. A family study of vesicoureteric reflux. J Med Genet 1978; 15: 85-96.

32) Menezes M, Puri P. Familial vesicoureteral reflux-is screening beneficial? J Urol 2009; 182: 1673-1677.

33) Alsaywid BS, Saleh H, Deshpande A, Howman-Giles R, Smith GH. High grade primary vesicoureteral reflux in boys: long-term results of a prospective cohort study. J Urol 2010; 184: 1598-1603.

34) Hannula A, Venhola M, Renko M, Pokka T, Huttunen NP, Uhari M. Vesicoureteral reflux in children with suspected and proven urinary tract infection. Pediatr Nephrol 2010; 25: 1463-1469.

35) Vachvanichsanong P, Dissaneewate P, McNeil E. Primary vesicoureteral reflux: a 26-year experience in a single centre. Nephrology (Carlton) 2016; 21: 335-340.

36) Ross MD. Update on vesicoureteral reflux: pathogenesis, nephropathy, and management. Rev Urol 2001; 3: 172-178.

37) Arlen AM, Kirsch AJ, Leong T, Cooper CS. Validation of the ureteral diameter ratio for predicting early spontaneous resolution of primary vesicoureteral reflux. J Pediatr Urol 2017; pii: S1477-5131(17)30072-4.

38) Devore JL, Berk KN. Modern mathematical statistics with applications. 2nd ed. New York: Springer; 2011.

39) Jang HC, Lee KH, Park JS. Primary vesico-ureteral reflux: comparison of factors between infants and children. Korean J Urol 2011; 52: 206-209.

40) Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. Br J Urol 1997; 80: 319-327.

41) Moore SS, Bahat H, Rachmiel M, Ziv-Baran T, Youngster I, Goldman M. Guidelines for urinary tract infections and antenatal hydronephrosis should be gender specific. Acta Paediatr 2015; 104: e512-517.

42) Estrada CR Jr, Passerotti CC, Graham DA, Peters CA, Bauer SB, Diamond DA, Cilento BG Jr, Borer JG, Cendron M, Nelson CP, Lee RS, Zhou J, Retik AB, Nguyen HT. Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. J Urol 2009; 182: 1535-1541.

43) Gearhart JP, Rink RC, Mouriquand PDE. Pediatric urology. 2nd ed. Philadelphia: Saunders, Elsevier, 2010.

44) Roberts JA, Riopelle AJ. Vesicoureteric reflux in the primate: II maturation of the ureterovesical junction. Pediatrics 1977; 59: 566-568.

45) Kang KM, Kim BS, Kim TH, Chung SK. The value of estimation of distal ureteral dilatation in primary vesicoureteral reflux. Korean J Urol 2010; 51: 354-357.

46) Tamminen-Möbius T, Brunier E, Ebel KD, Lebowitz R, Olbing H, Seppänen U, Sixt R. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. J Urol 1992; 148: 1662-1666.

47) Huang FY, Tsai TC. Resolution of vesicoureteral reflux during medical management in children. Pediatr Nephrol 1995; 9: 715-717.

48) Routh JC, Bogaert GA, Kaefer M, Manzoni G, Park JM, Retik AB, Rushton HG, Snodgrass WT, Wilcox DT. Vesicoureteral reflux: current trends in diagnosis, screening, and treatment. Eur Urol 2012; 61: 773-782.

49) Springer A, Subramaniam R. Relevance of current guidelines in the management of VUR. Eur J Pediatr 2014; 173: 835-843.

50) Cara-Fuentes G, Gupta N, Garin EH. The RIVUR study: a review of its findings. Pediatr Nephrol 2015; 30: 703-706.

51) Lim R. Vesicoureteral reflux and urinary tract infection: evolving practices and current controversies in pediatric imaging. AJR Am J Roentgenol 2009; 192: 1197-1208.

52) Haid B, Roesch J, Strasser C, Oswald J. The method of urine sampling is not a valid predictor for vesicoureteral reflux in children after febrile urinary tract infections. J Pediatr Urol 2017; pii: S1477-5131(17)30105-5.

53) Arlen AM, Cooper CS. Controversies in the management of vesicoureteral reflux. Curr Urol Rep 2015; 16: 64.

54) Tullus K. Vesicoureteric reflux in children. Lancet 2015; 385: 371-379.

55) Blais AS, Bolduc S, Moore K. Vesicoureteral reflux: from prophylaxis to surgery. Can Urol Assoc J 2017; 11: S13-S18.

56) Murawski IJ, Maina RW, Malo D, Guay-Woodford LM, Gros P, Fujiwara M, Morgan K, Gupta IR. The C3H/HeJ inbred mouse is a model of vesico-ureteric reflux with a susceptibility locus on chromosome 12. Kidney Int 2010; 78: 269-278.

57) Uetani N, Bouchard M. Plumbing in the embryo: developmental defects of the urinary tracts. Clin Genet 2009; 75: 307-317.

58) Wennerström M, Hansson S, Jodal U, Stokland E. Disappearance of vesicoureteric reflux in children. Arch Pediatr Adolesc Med 1998; 152: 879-883.

59) Silva JM, Santos Diniz JS, Marino VS, Lima EM, Cardoso LS, Vasconcelos MA, Oliveira EA. Clinical course of 735 children and adolescents with primary vesicoureteric reflux. Pediatr Nephrol 2006; 21: 981-988.

60) Kelly H, Molony CM, Darlow JM, Pirker ME, Yoneda A, Green AJ, Puri P, Barton DE. A genome-wide scan for genes involved in primary vesicoureteric reflux. J Med Genet 2007; 44: 710-717.