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Review Article

The management of vesicoureteral reflux in children

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Epidemiology

Vesicoureteral reflux (VUR) is defined as retrograde flow of urine from the bladder to the ureter. It is usually asymptomatic but commonly found in children with urinary tract infection (UTI). The prevalence is about 1-2% in general pediatric population.[1] However, the prevalence in children with UTI is much higher, reaching 30-57%.[1, 2] Similar prevalence (45.8%) is also reported in CiptoMangunkusumo Hospital.[3]

Etiology

Primary vesicoureteral reflux

Primary VUR is a congenital lesion not associated with any underlying obstructive or neuromuscular phenomenon. It is suggested to be related to the failure of antireflux mechanism at the vesicoureteral junction (VUJ) resulting in regurgitation. This regurgitation can cause spread of infection from the bladder to the ureter and kidney. Once the infection has reached the pelviocalyceal system of the kidney, microorganism can invade the parenchyma through intrarenal reflux (IRR).[3] Primary VUR is usually detected during radiologic evaluation of children with UTI. It can also found prenatally by the finding of hydronephrosis.[5]

Congenital primary VUR is characterized by short intramural ureter length relative to its diameter. The normal ratio is 5:1,[6] however in some conditions, the ratio is less causing dysfunction of normal antireflux mechanism (**Figure 1**).

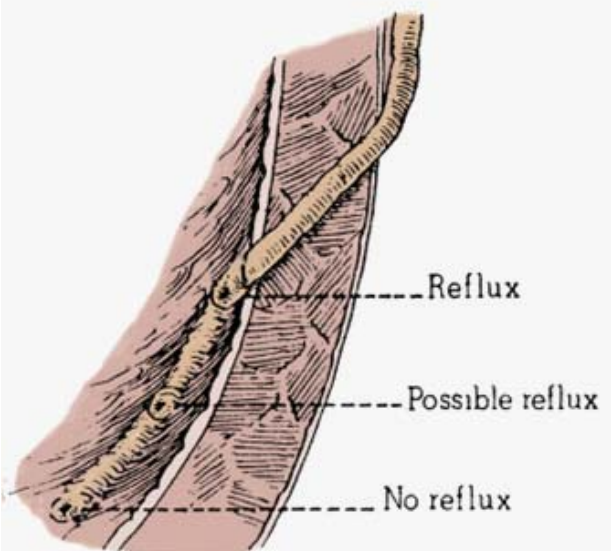

Figure 1. Vesicoureteral junction in normal state and reflux[6]

Secondary vesicoureteral reflux

Secondary reflux is not a congenital primary disorder. It is caused by anatomical or functional obstruction, bladder inflammation, or direct injury to orifice which is previously intact. It is suggested

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that the majority of low-grade reflux (grade I-III) is a secondary reflux which may improve with bladder maturation.[7]

One of the commonest cause of secondary VUR is voiding dysfunction, which is abnormality of one or more phase of voiding cycle. In a normal cycle, the bladder dilates as the urine fills in before contracts normally at voiding or emptying. During the filling phase, there should be no contraction or premature increase of pressure, while in the voiding phase, external urethral sphincter should completely relax so that urine will flow continuously until the bladder is emptied. Interrupted urine flow or incomplete emptying is a sign of voiding dysfunction.[8]

In children with voiding dysfunction, secondary VUR is usually resulted from the high bladder pressure. The high pressure can also cause the development of diverticulum which is a local outpouching of bladder wall due to muscular weakness. It also cause bladder dysfunction responsible for frequency or incontinentia symptoms.[8]

Patophysiology

Vesicoureteral reflux occurs due to increase of intrabladder pressure causing pathogen organism to be transmitted to the ureter and pelvis, or in severe cases, to the collecting duct and papillary tubules, a phenomenon called intrarenal reflux (IRR). Intrarenal reflux usually occurs in polar area. On voiding cystourethrogram (VCUG), it is characterized by the presence of contrast material in renal parenchyma, both in the collecting duct and nephron. Intrarenal reflux can result in formation of renal scar.[3, 6, 9]

Initial studies about IRR were conducted by Rolleston in 1974 and Rose in 1975 who observed reflux in neonates and infants. The studies revealed that renal scar is always formed in parenchyma segment exposed to IRR. Ransley and Risdon in 1975 also reported that scar is only formed in exposed area, either to infected urine or IRR.[6] Not all VUR result in renal scar. Low or moderate grade VUR do not increase the incidence of renal scar or UTI,[10] while the high grade one (grade IV-V) has the higher risk.[11]

Renal scar will cause arterial disruption and segmental ischemia, which in turn activates the renin-angiotensin system. The activation of this system, along with the abnormality of sodium transport due to reduced area containing the Na/K ATPase pumps and renal artery stenosis found in neuromuscular dysplasia, can result in hypertension.[12]

Hypertension occurs in up to 30% adult population in western countries, of which, 95% is idiopathic. Renal abnormality comprises a significant proportion in the etiology of hypertension in adult. Barai et al reported that VUR is found in 19.1% of adult population accidentally diagnosed to have hypertension without any obvious renal parencyma or vascular abnormality. This prevalence is tenth times of that was previously reported in children.[13]

Classification

In 1981, the International Reflux Study Committee established a reflux classification system. VUR is classified into five degree of severity based ureter and renal pelvicalyceal morphology seen in VCUG. The classification is useful for standardized description of reflux severity which is particularly important in clinical management, subject classification in research, clinical course documentation, and quantification of association between reflux and other clinical parameters that might affect the resolution of reflux.[2]

The classification of VUR severity is described as follows: grade I, backflow of urine into the ureter without any sign of dilatation; grade II, backflow of urine into the ureter and pelvicalyceal system without any sign of dilatation; grade III, mild to moderate dilatation of ureter dan renal pelvicalyces with minimal blunting of fornices; grade IV, moderate dilatation of pelvicalyceal system with turtuous ureter; grade V, severe dilatation of ureter and pelvicalyceal system, blunted round calyces, and severely dilated turtuous ureter **(Figure 2)**.

The characteristics of VUR

The main symptom of VUR is recurrent UTI which is often accompanied by fever. Other symptoms could be day or night incontinence; irritable symptoms

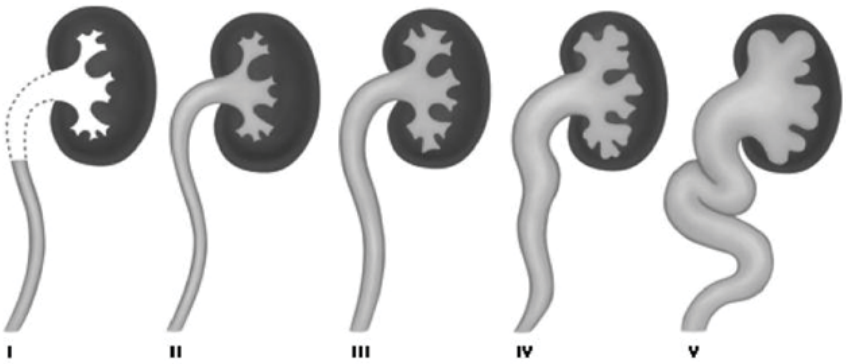

Figure 2. VUR degree of severity based on International Reflux Study.

such as frequency, urgency, and/or painful urination; obstructive symptoms such as hesitance, dribbling, intermittent and/or straining at urination; back, loin, or abdominal pain, and/or hematuria.[8] Proteinuria, nephrolithiasis, or hematuria during pregnancy can also be found.[14] Radiological examination shows unilateral or bilateral reflux in 30% of cases.

VUR can also be suspected by the presence of its complications, such as hypertension, voding dysfunction,[8] impaired renal growth, or chronic renal failure. Undiagnosed reflux can cause the formation of renal scar and reflux nephropathy (RN).[7] Those complications often occur in VUR patients with UTI.[5]

Reflux nephropathy is defined as focal renal scar in one or both kidneys due to primary VUR and UTI.[15] It is the most common etiology of childhood hypertension.[4, 16] In an England survey, the prevalence of RN is estimated to be 7-9% in children and adults.[4] In Cipto Mangunkusumo hospital, 85% of UTI children with VUR have already had reflux nephropathy, and 41% had experienced chronic renal failure.[3] In other studies, the prevalence of reflux nephropathy varied between 5-27%.[17] The prevalence of hypertension in reflux nephropathy is parallel to the severity of renal impairment and decreased function.[16]

However, VUR can resolve spontaneously in 45-60% of cases.[18, 19] In fact, the rate of spontaneous closure can be as high as 80% as the children grow older.[15] Hutch proposed the theory of intramural ureter maturation to explain the spontaneous resolution of reflux. As children grow older, the length of intramural ureter will also increase so that antireflux mechanism will function more properly.[3]

The association between VUR, voiding dysfunction, and UTI

Urinary tract infection can result in reflux. Inflammation occuring at the vesicoureteral junction and bladder wall can cause edema and loss of junction flexibility. Moreover endotoxin also can disrupt ureter peristaltic which results in incompetent vesicoureteral junction.[3] On the other hand, VUR is also a risk factor for recurrent UTI. Controversies exist regarding the effectivity of VUR surgical repair to overcome recurrent UTI since more than 40% of patients still experience recurrency after surgery.

Vesicoureteral reflux also can result from high intrabladder pressure due to voiding dysfunction.[8, 20] A previous study revealed that 26.6% of patients with voiding dysfunction experience VUR. Voiding dysfunction mainly occurred in female children with UTI. Indeed, it underlies the development of infection.[21] Many studies reported that the frequency of recurrent UTI is higher in children with voiding dysfunction compared to those without.[22] The improvement of voiding dysfunction decreases the incidence of UTI and enhances VUR resolution.[20]

Management of VUR

Several treatment choices are available, which are observation guarded by prophylactic antibiotic, endoscopy using dextranomer hyaluronic acid co-polymer (DxHA), and surgical correction. Ureteroneocystostomy is the gold standard therapy for VUR with success rate of 95% and 80% for grade

I-IV and grade V reflux, respectively.[23]

In Cipto Mangunkusumo Hospital, the management is determined according to the grade of reflux. Grade I and III is managed by conservative treatment. Children with grade IV-V VUR is managed by surgical repair. Ureteroneocystostomy is reserved for children aged more than 2 years old who do not show signs of intrabladder obstruction, recurrent intractable UTI, anomaly of ureter ostium (horseshoe or golf hole-like), or decreased renal function.[3]

Prophylactic antibiotics

Prophylactic antibiotic is basically given as an effort to keep the urine sterile while waiting for spontaneous resolution to occur. The rationale is that antibiotic can reduce bacterial colonization (especially *Enterobacteriaceae*) in urethral orifice to prevent the occurrence of ascending infection. To achieve this, ideally antibiotics should be broad spectrum and have high concentration in the urine with minimal influence on normal gut flora.[9] Common antibiotics for UTI eradication and prevention are listed on the following table.

Prophylactic antibiotics may prevent chronic renal failure due to recurrent UTI.[24] Meta-analysis showed that prophylaxis antibiotics have comparable outcome to surgery in reducing the risk of permanent or chronic renal failure. Various outcomes have been reported in mild VUR, but in severe VUR, prophylactic antibiotics are recommended, especially for those waiting for surgery schedule.[24, 25] However, long-term study found that neither medical treatment nor surgery is superior to each other. Moreover, contradictive results were reported in both treatment approaches. No treatment was proven to be effective for preventing the progression of chronic renal failure, but one study showed that early medical or surgical treatment can prevent recurrent injury to renal parenchyma. [24] The true benefit of surgery or antibiotic treatment might lay on its role in preventing UTI, but they are probably not adequately effective in preventing permanent chronic renal failure. Thus, the main goal of therapy is to prevent the renal parenchymal injury, no to cure the reflux.[26] Considering the possibility of spontaneous resolution of reflux, long term antibiotic prophylaxis is the main treatment to prevent recurrent UTI which can involve renal parenchyma (pyelonephritis) and cause permanent renal damage. However, it should be remembered that older children and high-grade reflux have lower possibility of spontaneous resolution.[27]

Table 1. Antibiotic dosage for treatment and prevention of UTI in children[3]

Type of drugs	Dose mg/ kg/day	Frequency (Age)	Prophy-laxis mg/kg**
Parenteral			
Ampicillin	100	Every 12h (<1 wk old)	
		Every 6-8h (>1 wk old)	
Cefotaxime	100	Every 8h	
Gentamicin	5	Every 12h (<1 wk old)	
	7.5	Every 8h (>1 wk old)	
Oral (first-line)			
Amoxicillin	20-40	Every 8h	
Ampicillin	50-100	Every 6h	
Cephalexine	50	Every 6-8h	
Nitrofurantoin*	5-7	Every 6	1-2
Sulfisoxazol*	120-150	Every 6-8h	50
Trimethoprim*	6-12	Every 12h	2
Sulfametoxazol	30-50	Every 12h	10
Nalidixic acid*	50	Every 12h	20

*Not recommended for newborns or renal insufficiency patients

**For prophylaxis: single dose at night (to achieve higher concentration in urine)

A study in Paris comparing the use of long (8 days) and short duration (3 days) ceftriaxone for children with acute pyelonephritis found that the incidence of renal scar is not different.[28] The comparison of oral to intravenous cephalosporin also did not result in different outcomes. Neuhaus reported that oral single-dose ceftibuten for 14 days compared to intravenous ceftriaxone or ceftibuten had comparable outcomes in children aged 6-16 years with acute pyelonephritis diagnosed based on DMSA.[29]

Another alternative treatment is the use of prophylactic probiotic in children with primary VUR. Lee et al reported that it has comparable effectiveness compared to antibiotic.[30]

A randomized controlled trial in Italia evaluated the effectiveness of 2 year course of prophylactic trimethoprim/sulphamethoxazole in 100 patients with grade I-III VUR. It revealed that the occurrence of pyelonephritis or renal scar at the end of 4-year follow up was not different between the antibiotic and placebo group.[31] Another study also reported that the use of prophylactic antibiotics did not reduce the recurrency of UTI after first episode, either in children with or without primary VUR.[32] A French study also found that prophylaxis antibiotics could

not reduce the incidence of UTI in children with low-grade VUR.[33]

Cotrimoxazole or nitrofurantoin can be given in single dose. Cotrimoxazole is often given as initial drug. Trimethoprim itself is reported to be as effective as trimethoprim-sulphametoxazole. Trimethoprim is excreted slowly through the prostate or vaginal secretion thus preventing periurethral contamination while nitrofurantoin is excreted rapidly through urine and its antibactrial effect will disappear after 8-12 hours. Some centers prefer to use cephalexin in children with G6PD deficiency. Amoxicllin, nalidixic acid, and quinolones are not recommended to be used as prophylactic antibiotics since resistance of gut flora might develop.[9]

Endoscopy

Endoscopy has been reported as the first-line treatment for VUR. Endoscopy-guided hyaluronic acid/dextranomer injection into ureter orifice is increasingly used as antireflux treatment as medical treatment with prophylactic antibiotics results in bacterial resistance while open surgery poses greater risk of morbidity.[34]

Chung et al suggested the use of Deflux injection as the first treatment of choice for VUR in children. Deflux, which was first introduced in 1984, is a bulking agent injected into ureter orifice or bladder subtrigonal area using endoscopy. It works by creating solid buffer behind intrabladder ureter and lengthening the intramural ureter (Figure 3 and 4).[27] Deflux is the most frequent agent studied. Other agents include teflon, silicone, bovine collagen, and polyacrylate polyalcohol copolymer. Most centers reported the success rate of Deflux injection is more than 70%, while long-term failure rate varies between 7-91%. Succes therapy is more common in low-grade reflux.[27, 35, 36]

The use of dextranomer hyaluronic acid co-polymer (DxHA) is very recommended for grade I-II VUR. Its usage has also been reported in complex VUR with duplex ureter or paraureteral diverticulum with success rate of 85% and 81%, respectively. Since the introduction of DxHA, endoscopy is often preferred over open surgical ureter reimplantation to treat VUR. The complication of DxHA injection is the formation of mound calcification at ureter orifice which can obscure the diagnosis of distal ureter stone.[37-40]

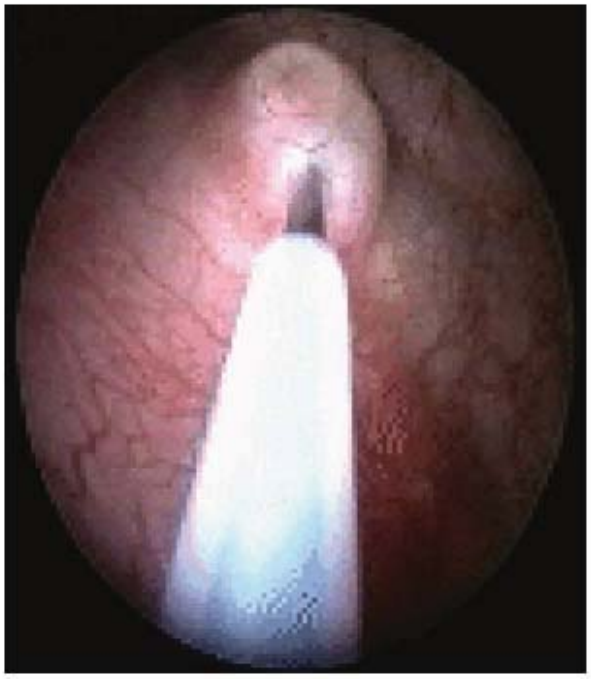

Figure 3. Ureter orifice as shown by 'rigid cystoscopy' during injection of periureter area

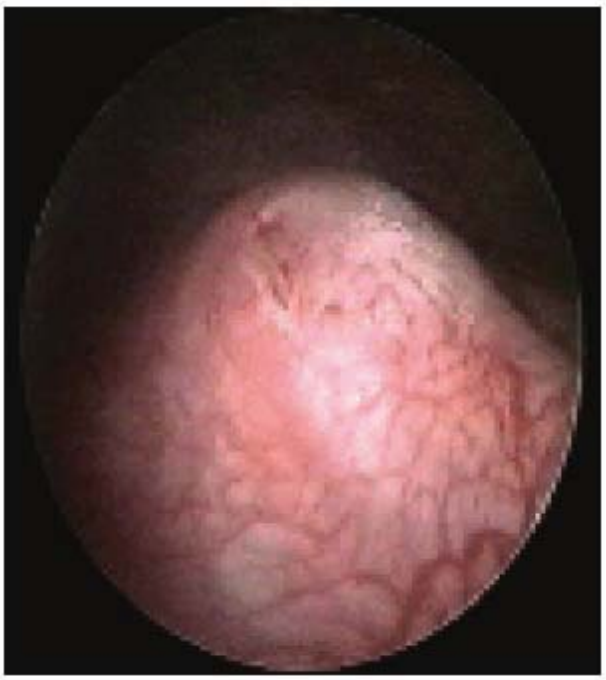

Figure 4. Injection was stopped after volcano-like appearance obtained

Another method of treatment is to reimplant the transtrigonal intrabladder ureter using CO2 pneumobladder laparoscopy. The procedure uses three trochars which are introduced into suprapubic area. After ureter is taken out from the bladder, the submucosa is incised, then ureter is reimplanted using absorbable 5/0 or 6/0 thread. Bladder drain is kept until 2-3 post-operative day. The success of the procedure is evaluated by USG and/or VCUG. Success rate of 92% has been reported.[41]

Open surgery

Children with recurrent ISK and progressive renal impairment, especially those with severe VUR, are recommended to undergo surgical correction besides receiving antibiotic prophylaxis.[25] Somogyi et al classified surgical procedure into temporary or permanent. Temporary interventions (cutaneous ureterostomy, percutaneous transrenal drainage) aim to reduce obstructive symptoms and VUR until definite procedure can be performed in optimal condition. Permanent surgical procedure is done by reimplanting ureter and excision of narrowed distal ureter segment using Politano-Leadbetter or Cohen technique.[42]

Ureter implantation is the treatment of choice for VUR. Both extra- and intrabladder reimplantation can be performed by surgery or laparoscopy. Lich-Gregoir technique is more easy to perform and require shorter time than Politano-Leadbetter, moreover by this technique gross hematuria can be avoided. This extrabladder approach also reduce post-operative pain and bladder spasm resulting in lower morbidity, making the Lich-Gregoir technique become the procedure of choice for unilateral VUR.[43] In bilateral reflux, two-stage Psoas-Hitch technique is performed to avoid bladder dysfunction.[7]

The main complication of extrabladder reimplantation is voiding dysfunction. Recurrent UTI, progressive renal scar, hypertension, and gestational hypertension are long term complications that may occur.[35, 44]

Simforoosh et al reported their success in performing trigonoplasty laparascopy using technique similar to Gil-Vernet open procedure. The success rate achieved 93% in grade II-IV VUR. In Gil-Vernet technique, distal ureter orifice is minimally dissected and approximated into the midline.[35]

Intractable VUR may be managed by open surgery. Extrabladder ureteroneocystostomy is a safe and effective procedure for this condition. Indeed, some authors reported that ureteroneocystostomy can be performed by minimal incision (2 cm length) at the inguinal area (mini-ureteroneocystostomy) with 82% success rate. In high-grade (III-IV) VUR, this procedure has higher success rate compared to DxHA (100% vs. 78%, p = 0.002).[45, 46] Psoas-Hitch technique is performed in patients with persistent reflux or obstruction whose previous ureteroneocystostomy failed to correct the disorder.[47]

Problems

Children suffering from VUR who are not treated develop renal scar and at least 10% of them had hypertension.[48] Hypertension can enhance the progression of chronic renal failure causing 10-20% of children have to undergo renal transplantion. This problem requires an effective and feasible guidelines for VUR management.[9]

Treatment modalities for VUR in children consist of long term antibiotic prophylaxis and/or laparascopic or open surgical procedure. Conservative treatment with prophylactic antibiotics can preserve renal

Table 2. The rate of UTI according to treatment modalities

Authors	Setting	Publication year	Study duration	Intervention	N	UTI (%)		P
						AB	No AB	
Jodal	Germany	2006	10 year	AB vs. surgery	306	25.2	13.6	<0.03
Lee	South Korea	2007	6 month	AB vs. probiotic	120	21.6	18.3	0.926
Pennesi	Italy	2007	2 month	AB vs. no treatment	100	18	16	0.71
Montini	Italy	2008	12 month	AB vs. no treatment	338	7.1	9.5	>0.05
Roussey-Kesler	French	2008	18 month	AB vs. no treatment	225	17	26	0.2

Note: AB = prophylaxis antibiotic

Table 3. Renal scar formation according to treatment modalities

Authors	Setting	Publication year	Duration	Randomization	N	Scar formation (%)		P
						AB	No AB	
Jodal	Germany	2006	10 years	Antibiotic vs. surgery	306	48.8	49.6	>0.05
Lee	South Korea	2007	6 months	Antibiotic vs. probiotic	120	15.4	9.1	0.596
Pennesi	Italy	2007	2 months	Antibiotic vs. no treatment	100	40	36	0.4
Montini	Italy	2008	12 months	Antibiotic vs. no treatment	338	1,1	1,9	>0.05
Bouissou	French	2007	9 months	Long vs. short-term antibiotic	386	17	13	>0.05
Neuhaus	Switzerland	2007	6 months	Intravenous vs. oral antibiotic	365	45.8	26.3	0.2

Table 4. Outcomes of endoscopy technique

Name	Setting	Publication year	Study Duration	Methods	N	Success rate (%)	Mean length of stay (days)
Nelson	USA	2009	1 years	Endoscopy vs. open surgery	9.496	-	2.0
Chung	Hong Kong	2009	3 months	Deflux injection	42	85.9	3.4
Ormaechea	Brazil	2010	1 years	Polyacrylate polyalcohol (PPC)	83	83.6	-
Molitierno	USA	2008	3 months	Dextranomer hyaluronic acid co-polymer (DxHA)	52	85	-
Dave	Canada	2008	3 months	DxHA	126	50	-
Lee	USA	2009	1 years	DxHA	219	46.1	-
Valla	French	2009	24 months	Cohen transvesicoscopic ureter reimplantation	72	92	2.8

Table 5. Success rate of open surgery technique

Name	Setting	Publication year	Technique	N	Male	Female	Ureter reflux (Unit)	Mean age	Success rate (%)
Simforoosh	Iran	2008	Trigonoplasty	65	56	9	103	5,68	94.1
Ashley	USA	2008	Mini-	57	48	9	57	4,0	100
Mor	Israel	2003	Politano-Leadbetter and Glenn-Anderson advancement	100	21	79	146	6,0	51
Schwentner	Austria	2006	Lich-Gregoir vs Politano-Leadbetter	44	29	15	44	5,5	98

function by keeping the urine sterile and preventing recurrency of infection. This treatment goal also can be achieved by surgical procedure, however whether medical or surgical management is superior to each other still become a continuing debate.[49, 50] The risk of antimicrobial resistance posed by long-term prophylactic antibiotics makes surgical correction become the treatment of choice, and since antireflux implant was introduced in 2001, laparoscopic surgery is preferred over open procedure.[25, 34]

Follow Up

All VUR patients must have regular examination during therapy, and whenever required, imaging evaluation should be done. The role of imaging is to detect spontaneous resolution, monitor the formation of new renal scar, detect abnormal kidney growth, and monitor renal function.[3]

It is recommended to VCUG evaluation 3 months after surgery which can be repeated 4-6

weeks afterward or if obstructive symptoms recur. Initial screening is done with ultrasonography to assess the progression or hydronephrosis and grossly evaluate the renal parenchyma/cortex, blood pressure examination, urinalysis, urine culture, as well as serum ureum and creatinine. It is recommended to perform those examinations every 3 months. Patients with renal scar are recommended to have renal scintigraphy evaluation at 12 months after starting therapy and have routine blood pressure monitoring.[6]

Conclusions

Vesicoureteral reflux is defined as retrograde flow of urine from baldder to ureter. The prevalence in children is about 1%. It is usually asymptomatic but commonly found in children showing UTI symptoms with a prevalence of 30-75%. Untreated children may develop renal scar, reflux nephropathy, hypertension, voiding dysfunction, retarded kidney growth, and chronic renal failure.

The management include observation guarded by prophylactic antibiotic, endoscopy using dextranomer hyaluronic acid co-polymer (DxHA), and open surgical correction. Prophylactic antibiotics can not reduce the prevalence of renal scar formation. Early surgical correction may prevent UTI. Endoscopy is now preferred for surgery considering its lower morbidity compared to open procedure and high success rate (92%). However, open surgery still has the highest success rate which can reach 100%.

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