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Personal Practice

Current Concepts of Urinary Tract Infection and Vesicoureteric Reflux in Children

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Abstract Recent literature has clarified the relationship of UTI, VUR and renal scarring but their management is still controversial. The overall prevalence of UTI among febrile infants is 5%. For proper management, a firm diagnosis by demonstrating positive cultures of bladder tap or catheterised urine samples is essential. Imaging strategies following a first UTI aim at detecting underlying urological abnormalities, VUR and scarring, but protocols vary. There is general agreement (1) to fully investigate all infants under 1 year and all children with recurrent UTI, and those with abnormal clinical/laboratory features suggestive of urological problems; and (2) not to investigate girls older than five years. In between, the "aggressive" nephrologists investigate all boys of any age, and all children below five years. The "conservative" will do USG+DMSA for these patients, reserving MCU for those with abnormal findings. Among the risk factors for renal scarring, voiding dysfunction and host inflammatory response are two subjects under intensive research. In addition to prophylactic antibiotics, recent trends in management recommend (1) early and prompt antibiotic treatment for any febrile UTI and non-treatment of asymptomatic bacteriuria. (2) looking for and correcting constipation, bladder instability and detrusor-sphincter-dyssynergia. (3) doing circumcision for boys with recurrent UTI. The role of ureteric reimplantation has been reviewed by American Urological Association and is summarised.

Key words Reflux nephropathy; Ureteric reimplantation; Urinary tract infection; Vesicoureteric reflux; Voiding dysfunction

Introduction

Urinary tract infection (UTI) is a common infection in children. Its importance lies in its frequent association with urological abnormalities, notably vesicoureteric reflux (VUR); and its proneness to recur. These factors cause renal scarring, which is thought to predispose to hypertension and end-stage renal disease (ESRD) in adults. The purpose of management is to identify and treat all cases of UTI, detect underlying abnormalities, prevent recurrence and hopefully prevent renal scarring and the adverse outcomes. On the other hand, one must distinguish those children at low risk of these problems to spare them from the invasive investigations and unnecessary treatment. This article attempts to summarise the current concepts in pathogenesis of UTI and renal scarring, as well as in diagnosis and management of this common renal problem.

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Prevalence of UTI

Three recent publications gave data on prevalence of UTI from different perspectives. A meta-analysis of mainly published cross-sectional studies by American Academy of Pediatrics (AAP) reported a pooled prevalence of 5% among febrile children aged between three months and two years.[1] In an epidemiological study from Sweden, Marild and Jodal found a cumulative incidence of 6.6% in girls and 1.8% in boys up to the age of 6 years. The annual incidence was between 0.9% to 1.4% each year in girls, but in boys, it was 0.8% in infancy and only 0.1% beyond one year of age.[2]

Shaw et al studied the prevalence of UTI among infants and girls younger than two years who presented to Emergency Department with documented fever without identifiable source.[3] They found that the overall prevalence of UTI was 3.3%, but the prevalence was much higher in certain high risk groups: namely girls, the white race,

infants, patients with clinical parameters like the absence of potential source of fever, appearing ill, high fever of >39°C, any urinary symptoms or abdominal tenderness. The absence of circumcision and a past history of UTI also predispose these children to UTI.

Pathogenesis of UTI

Why do some children develop UTI and others do not, and why do some have recurrent UTIs? The pathogenesis of UTI is believed to involve the following events: Pathogenic bacteria originating from the patient's own gut flora first colonise the peri-urethral area. It then ascends to proliferate in the bladder and starts the process of tissue invasion and infection.[4] In normal circumstances, this is prevented by regular emptying of the bladder to clear any bacteria present and the patients own immune defences. However in the presence of incomplete emptying such as occurring with dysfunctional voiding, neurogenic bladder, and VUR, residual urine occurs and the bacteria cannot be washed away. Prior antibiotic treatment may eradicate the benign commensals and allow virulent bacteria to invade into their territory. Boys without circumcision have bacterial colonization of their foreskin, predisposing them to infection. Individuals with proneness to UTI were also found to be non-secretors of blood group substances, to have higher density of fimbrial receptors in their gut epithelium and to have decreased urinary IgA concentration.[5]

Almost all cases of first time UTI are caused by E.coli. These gram -ve bacilli are ideally suited to cause UTI. Their rigid cell wall protects them from the hyperosmotic urine. They possess P-fimbriae which adhere to receptors on surface of uroepithelial cells. They release lipopolysaccharides which are the endotoxins that provokes the host inflammatory or sepsis response.

Thus the bacterial toxins promotes chemotaxis and activation of granulocytes. This is followed by release of free oxygen radicals and lysosomal products, which causes tissue damage and death and later replacement by fibrosis and scarring. These processes have been indirectly proven by observing the effects of various drugs on the histopathology of pyelonephritis in animal experiments: Antibiotics can decrease bacterial count, renal swelling, polymorph infiltration and prevent chronic scarring. Colchicine, which inhibit chemotaxis, and cyclophosphamide which decrease the white cell counts, did not stop bacterial invasion but prevents renal swelling, inflammatory exudates and tissue scarring. Dapsone, allopurinol and superoxide dismutase (which reduce the oxidative bursts and inhibit protease activity) prevents tissue scarring but had no effect on renal oedema and polymorph infiltration.[6]

Risk Factors for Renal Scarring

Why do some children develop renal scars after pyelonephritis while others do not? The following risk factors have been reported in the literature.

Obstructive Uropathy

Infection in the presence of obstruction causes rapid renal damage and scarring. Even without infection, gross VUR due to high pressure obstruction, such as those created by bladder neck ligation in the animal experiments of Hodson et al. in 1975, had been shown to cause generalised cortical thinning of the kidneys.[7]

Vesicoureteric Reflux (Especially Intrarenal Reflux)

A recent review by AAP suggested that VUR occurs in 30% to 40% of children investigated for first-time UTI. The prevalence is high (about 50%) in infancy, levels off to 30% at one to five years and then falls off. Renal scars have been reported in up to 40% of such kidneys. Actually the risk of having scars is directly related to the severity of reflux. Those children with high-grade VUR had eight to 10 times higher risk than those without VUR, and four to 6 times higher risk than low grade VUR.[8] This form of renal scarring is manifested as segmental scars occurring mainly over the concave or flat papilla where the ducts open end-on to the renal pelvis so that intrarenal reflux can occur at these sites, transmitting infection into the renal parenchyma. Nevertheless VUR is not the predominant factor because renal scars as detected by DMSA scan were as frequent in patients with VUR as in those without VUR.[9]

Young Age at UTI

UTI is commoner in young children and the majority of renal scarring was detected on investigation of first-time UTI. However there are still controversy as to the age limit above which scarring will not occur. Smellie et al. collected 74 children from 23 centres in UK, who had developed new scars or progression of existing scars after initial evaluation: 34% of these children did so after five years old, and three children had new scars as late as 10 years old. The scarring was correlated to grades of VUR, history of UTI and delay in starting treatment for UTI.[10]

In another more recent publication, Vernon studied the rate of new scars in those children who had normal DMSA scans at three and four years old. They reported that the group with normal initial scan at four years old developed no scarring on follow up, while the group with normal scan at three years old did develop scarring in 2.9% of cases. This suggested that new scars will not occur after four years old.[11]

Nevertheless we must be aware that if patients already

had scarring at initial investigation, new scarring can occur at any age.

Renal Dysplasia Due to In-utero VUR

Yeung et al from London reported their study of a large cohort of 155 infants, aged three days to seven months, who were referred for investigation of prenatal hydronephrosis and subsequently found to have VUR.[12] They described two common patterns of VUR: The first one is mild Grade I-III VUR occurring in 78% of girls and 46% of boys. The second pattern is severe grade IV-V VUR occurring in 22% of girls and 54% of boys. The VUR was associated with small contracted kidneys which predominantly occurred in the male babies. Yet 85% of these cases had never experienced UTI before the imaging studies. In another study, they reported evidence of renal dysplasia in the nephrectomy specimens from these patients, suggesting that this may be a form of renal dysplasia secondary to severe in-utero VUR.[13]

Delay in Diagnosis and Treatment

It is also well demonstrated in the piglet experiments of Ransley and Risdon that scarring could be prevented by prompt and effective treatment within seven days of introducing the infection.[14] Also retrospective analysis of 52 cases of new or progressive scarring by Smellie showed that in 50 cases, there was a history of delay in diagnosis and treatment of UTI or follow-up investigations.[15]

Recurrent Episodes of UTI

Jodal et al. showed that the risk of renal scarring increased exponentially with the number of episodes of UTI.[16]

Presence of Voiding Dysfunction

In recent years, a popular area of research is the relationship between voiding dysfunction and UTI. In a branch study of the International Reflux Study in Children, 310 children below 5 years old were interviewed and 18% complained of symptoms of urgency, interrupted stream, incomplete voiding or postponement of stream. These children had more symptomatic UTI and less resolution of VUR compared with those without voiding dysfunctions.[17]

Bachelard et al. used video-cystometry to study 90 boys and 68 girls with UTI and detected unstable bladder in two-third of cases, manifested as high voiding pressure and low bladder capacity.[18]

Koff et al. described the "dysfunctional elimination syndrome (DES)" in which children suffered from a combination of bladder instability, constipation and infrequent voiding.[19] In 143 children with primary VUR, 43% had DES. These patients had more breakthrough UTIs, delayed resolution of VUR, persistent UTI despite resolution of VUR or its correction by surgical reimplantation. VUR may also recur or appear in the contralateral system after surgery.

Host Factors

Another hot area of research is the role of host response to UTI in causing renal scarring. Cytokines have been extensively studied in UTI.[20] It has been reported that the proinflammatory cytokines like interleukin-8 (IL-8), interleukin-6 (IL-6), and interleukin-1 (IL-1) were increased in the urine of children with acute pyelonephritis, and higher levels was found in infants and first-time UTIs. When reassessed after one year, only IL-6 levels were correlated to the degree of renal scarring. On the other hand, the downregulatory cytokines showed two different patterns: The IL-1 receptor antagonist, soluble IL-6 receptors were found to be decreased while the soluble tumour necrosis factor (TNF)-receptors I & II were increased. However at present it is still too early to say if they have any use in predicting renal scarring.

On the other hand, renal scarring has been found to be associated with certain angiotensin converting enzyme (ACE) gene polymorphism. The ACE gene converts angiotensin I to angiotensin II which produces interstitial fibrosis and glomerulosclerosis by causing local vasoconstriction, stimulating transforming growth factor β (TGFβ) production and stimulating collagen synthesis. It has been reported by Ozen et al. that individuals with the DD genotype (which causes increased ACE activity) is associated with 4.9 times higher risk of renal scarring.[21] In animal studies, treatment with ACE inhibitors or Angiotensin II receptor blocker Losartan could reduce TGFβ mRNA expression and reduce the interstitial and glomerular fibrosis in chronic renal diseases.

Can Renal Scarring Lead to Endstage Renal Disease and Hypertension?

The answer is probably yes but the evidence is not strong. In cohort studies, ESRD develops in 3% to 10% of those with extensive scarring; and hypertension occurs in from zero to 50% of these patients. Also a significant proportion of ESRD patients were related to pyelonephritis. For instance, data from the European registry of renal failure showed that 36% were due to obstructive uropathy, renal hypo/dysplasia and pyelonephritis.[1] In Hong Kong a survey of chronic renal failure in children in 1993 showed that 18% were due to chronic pyelonephritis.[22]

Nevertheless we should be aware that there are at present no longitudinal data that directly link the presence of VUR and febrile UTI in children with normal kidneys

to the subsequent development of hypertension or ESRD.[23]

How Should UTI Be Diagnosed?

The diagnosis of UTI needs confirmation by positive bacterial culture. In young children, the interpretation of urine culture depends on the method of collection.

The suprapubic tap urine is considered the gold-standard, with any positive growth being diagnostic of UTI. The disadvantage is that it is invasive and not always successful. The success rate of a blind tap varied from 36% to 60% but this can be enhanced to over 90% by ultrasound confirmation of a full bladder or real-time USG guidance.[24,25]

The difficulty with catheterised urine culture is that the criteria used by different groups varied from 1,000 cfu/ml to 50,000 cfu/ml. A recent review by the AAP reported that if 1000 cfu/ml was used as cutoff, its sensitivity was 95% and specificity was 99%.[1] It is an acceptable alternative to suprapubic tap. However there is still a chance of contamination in uncircumcised boys, and it carries a definite risk of introducing infection. Therefore, some authors recommend to reserve it for cases where we want to get a proper urine sample for culture before starting antibiotic therapy.

The clean catch urine culture was accepted by the Royal College of Physicians Guidelines in 1990 and the cutoff used was $>10^5$ cfu/ml.[26] Other authors such as Hellerstein used a lower cutoff of 10^4 for boys.[27] Recent studies have shown that infants may have a lower bacterial count - 20% of 366 infants with UTI proven by suprapubic tap has counts below 10^5/ml.[28]

The bag urine is a convenient and non-invasive method of collection. It has been used to exclude UTI when demonstrating cultures of $<10^4$/ml, but as we have said earlier this may not be valid. There is also a high false positive rate with specificity only between 14% to 84%. The AAP advised against its use for diagnosing UTI. It is mainly used to collect urine for the rapid bedside test.

Can we make a rapid bedside diagnosis and start early treatment? The AAP has reviewed the test characteristics of leucocyte esterase, nitrite, microscopy for leucocytes and gram smear for bacteria. They reported that each test has a sensitivity and specificity of roughly 80%. However if these tests are used in combination and any positive result was taken as positive, the sensitivity approaches 100% and specificity was 70%, suggesting that they can be used to pick up all UTI cases, but they still need culture to confirm the diagnosis.[1]

There are three recent papers comparing the cost-effectiveness of alternative strategies for detecting UTI in young children. Kramer et al. in 1994 recommended to send catheterised urine cultures for all children with temperature above 39°C and, while waiting for results, to treat those with positive urinalysis.[29] This approach was the least costly, and has a preventive fraction of zero point four five, meaning that this strategy can prevent 45% of adverse outcomes of UTI.

Shaw et al. in 1998 recommend sending bladder tap or catheterised urine culture for all febrile children while treating those with positive urinalysis.[30] If they do just the dipstix for urinalysis, the cost was lowest (US$3.7 per patient) but seven out of 1000 UTI cases will have delayed treatment. If they do dipstix plus microscopy, the cost was doubled but there was no cases of delayed treatment.

The latest review by the AAP recommended two approaches.[1] The first one was sending catheterised or tap urine culture for all. The second one was doing dipstix and microscopy for all and only send catheterised or tap urine culture for the positive cases. They found them to be equally effective and the latter is less costly.

What Should Be the Follow Up Investigations After First Time UTI in Children?

The purposes of investigations are to detect underlying anatomical abnormalities of the urinary tract, to look for VUR, to assess renal functions and degree of scarring of each kidney, and to look for bladder dysfunction. The choice of each test depends on its sensitivity of picking up the abnormalities, its degree of invasiveness and dose of irradiation. The ultrasonogram (USG) is best at detecting anatomical anomalies and kidney sizes. The dimercaptosuccinic acid scan (DMSA) is most sensitive at picking up renal scars and also give differential renal function. The intravenous urogram (IVU) can assess kidney sizes, scarring and differential function but it is seldom used because of the difficulty in getting good images in infants. The micturiting cystourethrogram (MCU) can detect urethral and bladder anatomy, detect VUR and grade its severity. Bladder dysfunction is best shown by a formal urodynamic study. Usually a combination of tests has to be performed to identify all potential abnormalities.

There are wide variations in the imaging protocols after UTI.[26,31-34] It is generally agreed that complete investigations should be performed for all infants below one year and all children with recurrent UTI, those with abnormal clinical or laboratory or USG findings. By complete investigations, one will do USG plus MCU plus DMSA.

There is also no controversy that older girls above five years of age (or seven years according to Royal College of Physicians guidelines[26]) need no investigations except a noninvasive USG and plain KUB.

Controversies exist in investigating children between one and five years old. For girls, most authors recommended complete investigations for those below two years, and limited investigations for those above two years (i.e. just USG and DMSA, proceeding to MCU if these are abnormal. But others would perform complete investigations for all below five years; while on the other extreme others perform limited investigations for all in this age group.

Since UTI is very uncommon in boys above one year old, most would be more cautious to investigate boys. But again there are controversies. Most would recommend complete investigations for all boys. But some authors recommended complete investigations only for those below three years old and limited investigations for boys above three years old.

In fact, there is no evidence from randomised controlled trials to indicate whether one strategy is superior to another.

Management of VUR: The Role of Prophylactic Antibiotics

It is standard practice to recommend prophylactic antibiotics for children below five years old who have VUR, who have recurrent UTI; or who need instrumentation of the urinary tract. There are in fact no long term controlled trial comparing continuous prophylaxis versus intermittent treatment of acute episodes of UTI. The recent review by AAP suggested a 50% effectiveness of prophylaxis in reducing rates of reinfection or scar progression.[1]

A controlled trial by Smellie et al. of antibiotic prophylaxis versus no prophylaxis in 45 children showed significant reduction in the incidence of UTI during prophylaxis.[35]

According to the data of Leneghan, before antibiotic prophylaxis was routinely prescribed, 35% to 61% of UTI children had scarring at diagnosis, Of those with normal kidneys, 21% had new scarring, while of those with existing scars, 66% had new scars or further progression.[36] This can be compared to data from the post-prophylaxis era. For instance, Smellie et al. reported that only two kidneys among 75 children followed up for seven to 15 years had developed new scars.[37] The International Reflux Study in Children also reported a rate of new scarring of 35% in the European Branch, and 21% in the American Branch.[38,39] We must remember that patients in this study had more severe Grade III-IV VUR.

Management of VUR: The Role of Surgical Reimplantation

At least two large randomised controlled trials have been performed that showed no benefit of surgical reimplantation versus medical prophylaxis alone. The Birmingham Reflux Study Group involved 161 children below two years old with UTI and VUR (50% had scarred kidneys at entry). Overall, there were new scarring in 10 kidneys, and progression in 31 kidneys but they were evenly distributed in the medical and surgical group (6% versus 5.2%). There was no significant difference in the rates of breakthrough UTI.[40]

The International Reflux Study in Children involved 402 children from Europe and 136 children from USA with Grade III and IV VUR.[41] They found again no difference in the rate of breakthrough UTIs, new scars or scar progression between surgical and medical groups, though the medical group tend to have 2.5 times more of febrile UTI than surgical group.

Management of VUR: Expert Recommendations

The American Urological Association has attempted to issue practice recommendations for management of primary VUR in children.[42] Their literature review led them to conclude that firstly, primary VUR in children tends to resolve spontaneously. The probability of resolution is higher for young patients, low grade VUR or unilateral VUR (Figure 1). Secondly, there is no direct evidence that any treatment option is superior to another. Thirdly, in general, parental and patients preferences should be honoured. Their recommendations were mainly based on expert opinions, and were given as guidelines, preferred options or reasonable alternatives, according to the number of votes each received from the expert panelists.

For the infants under one year old, VUR should be managed by antibiotic prophylaxis initially. In infants with gross Grade V reflux and scarring, a reasonable initial alternative is surgical reimplantation.

For the children aged one to five years, antibiotic prophylaxis is generally the recommended initial treatment. In children with Grade V VUR with scarring, initial surgical treatment is a preferred option. For children with Grade V VUR without scarring, or those with Grade III-IV VUR with scarring, surgery is also a reasonable alternative.

When children become older (>5 years old), the chance of spontaneous resolution is minimal, and more urologists preferred surgery as the initial treatment for Grade V VUR without scarring, or Grade III-IV VUR with scarring or persistently severe VUR. However if the VUR is mild (i.e. Grade I-II), there is no consensus to their further management.

In all cases, surgery may be indicated at any time when there is failure of medical treatment as shown by recurrent symptomatic UTIs and non-compliance or intolerance to drug prophylaxis. Before surgery, especially in infants,

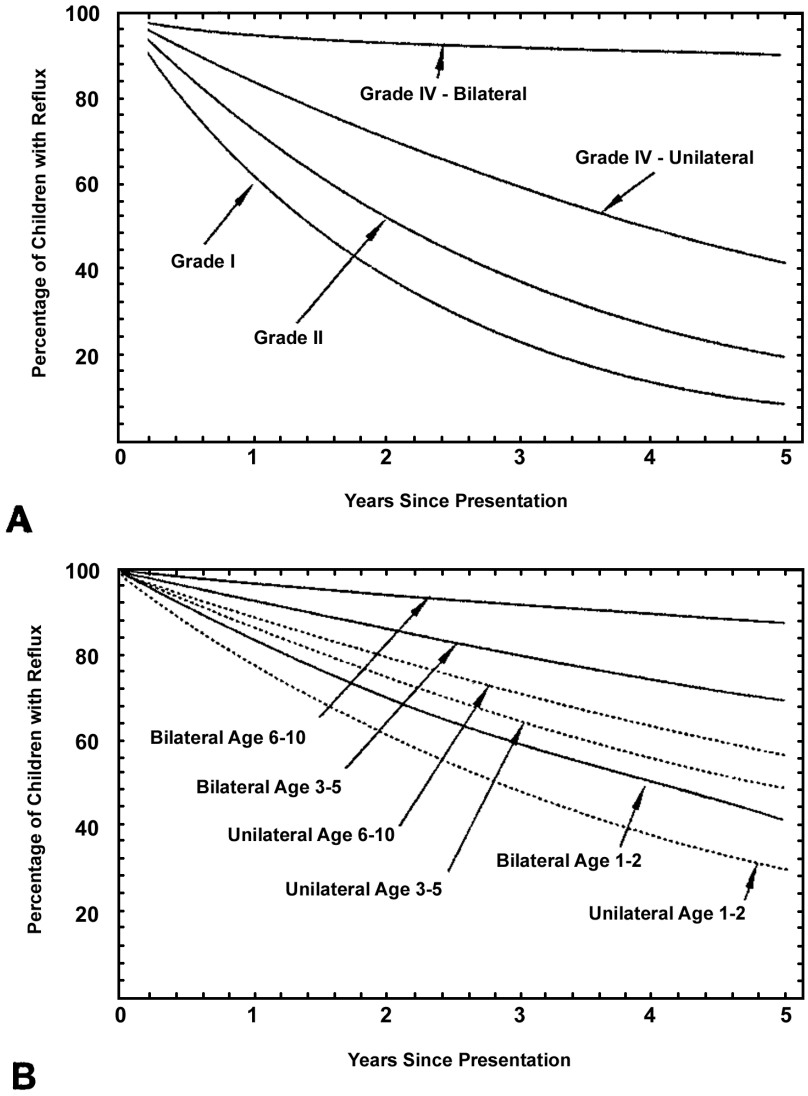

Figure 1 Percent chance of reflux persistence for 1 to 5 years following presentation. 1A, grades I, II, and IV reflux (bilateral and unilateral). 1B, grade III reflux by patient age at presentation. (reproduced from Elders et al.[42])

one needs to exclude voiding dysfunction by urodynamic study because this needs to be tackled before UTI can be prevented.

Conclusion

In summary, recent researchers have highlighted the important role of bladder dysfunction in causing UTI and of genetic predisposition to renal scarring. Recent cost-effectiveness analysis supported the use of combined dipstix and urine microscopy for screening of UTI followed by confirmation by proper urine cultures. There are still no universal protocol for investigations and follow up treatment for UTI and VUR. In general, each hospital has to develop its own protocol in relation to investigations and medical versus surgical treatment of children with VUR, taking into account the medical evidence available, the availability of resources, and local radiologists and surgeons' expertise.

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