

Congenital urogenital abnormalities in children

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Abstract

Congenital urogenital abnormalities cover a wide range of conditions, both anatomically and functionally, which may cause UTI, renal scarring and end stage renal disease. Obstructive uropathy seems to be one of the more important disorders to diagnose and follow to prevent UTI and deterioration of kidney function. However, evidence of exactly which anomalies pose the greatest risk and stand to benefit from either prophylactic precautions or surgery is still sparse. The available data for UTI and upper urinary tract obstruction suggest that continuous antibiotic prophylaxis (CAP) and possibly male circumcision reduce the incidence of pyelonephritis in infants with hydroureteronephrosis.

Keywords: urinary tract infection, children, obstructive uropathy

Summary of recommendations

1. There is no need for CAP in infants with mild renal pelvic dilatation as the resolution rate is high and the risk of UTI low (GoR B).
2. CAP is recommended during the first 6–12 months of life in infants with obstructive hydroureteronephrosis, especially with ureteric dilation >11 mm (GoR B).
3. In high risk urinary tract abnormalities circumcision needs to be taken into consideration when counselling parents (GoR C).
4. Surgery has to be undertaken whenever CAP fails or other signs of worsening of the obstruction occurs (GoR C).

1 Introduction

Over time routine prenatal ultrasound has detected an increasing number of fetal abnormalities among which the most common are of urogenital origin. Antenatal hydronephrosis (AH) is the most frequent reported congenital anomaly, occurring in 1–5% of all pregnancies [1]. Upper urinary tract dilatation may be associated with vesicoureteral reflux (VUR), obstructive uropathies, multicystic dysplastic kidney (MCDK) and congenital megaureter [2]. It is crucial to identify which of the AH will become clinically significant to prevent deterioration of renal function postnatally. If not recognized on prenatal ultrasound urinary tract anomalies may manifest later in life as pyelonephritis, hypertension or end stage renal failure.

Some studies have shown that infants with AH are at increased risk of postnatal urinary tract infection (UTI) [3] and that the risk increases with severity and persistence during the first year of life [3], [4], [5]. This underlines the importance of early diagnosis, planning of relevant follow-up as well as decision on the need for prophylactic initiatives or surgery.

There are many challenges and controversies regarding the extent of postnatal follow-up with regards to the timing and magnitude of tests needed to prevent irreversible damage of the renal parenchyma. Likewise, the need for antibiotic prophylaxis is an ongoing discussion, when it comes to deciding who, when and for how long. Another challenge is to determine if and when to operate, since many do well without surgery.

This chapter will focus on inborn urinary tract abnormalities in terms of definition, diagnosis, evaluation and management with special reference to UTI.

Inborn urogenital abnormalities are a heterogeneous group of abnormalities of the urinary tract and genitalia. The uropathy may be obstructive or non-obstructive. Obstructive uropathy is either an upper urinary tract obstruction, uretero-pelvic junction obstruction (UPJO), vesico-ureteral junction obstruction (VUJO) and primary non-refluxing obstructive megaureter (PNROM), or a lower urinary tract obstruction. Lower urinary tract obstruction may be an anatomical (posterior urethral valve, PUV) or a functional obstruction (neurogenic bladder or dysfunctional voiding). Non-obstructive uropathies are vesicoureteral reflux (VUR), MCDK and a subgroup of megaureters. Abnormalities of the genitalia are rarely obstructive and literature on the association between genital anomalies and UTI is scarce.

Vesicoureteral reflux and spina bifida are discussed separately in another section. Therefore, the main topics of this overview will focus on the upper urinary tract with special attention on hydronephrosis and obstructive uropathies.

2 Methods

A systematic literature search was performed for the last 20 years in MEDLINE and the Cochrane library with the following key words; congenital urinary tract anomalies, hydronephrosis, obstruction, megaureter, posterior urethral valve AND UTI with the following criteria: English publications, human studies, clinical trials, meta-analyses, review, randomized clinical trial, comparative study, ages birth to 16 years old.

A total of 77 publications were identified, which were screened by title and abstract. Finally, 20 publications were included into this review and supplemented by publications mentioned in the selected publications or known by the author.

The studies were rated according to the level of evidence (LoE) and the strength of recommendations graded (GoR) according to a system used in the EUA guidelines (2015) modified from the Oxford Centre for Evidence-based Medicine [6].

3 Results

Congenital obstructive abnormalities of the upper urinary tract that may cause UTI are rarely addressed in the literature with particular reference to UTI. The literature search has revealed a limited number of very heterogeneous studies with relative low level of evidence. There are no randomized studies and controlled studies are few.

3.1 Postnatal evaluation of antenatal hydronephrosis – clinical spectrum

The incidence of AH (defined as renal pelvic diameter (RPD) ≥ 5 mm) is 0.59–0.65% [8], [9]. Hydronephrosis does not necessarily imply obstruction nor does it say anything about the function of the affected kidney. Furthermore, there is evidence that many mild cases of AH spontaneously improve or resolve [4], [9], [10], [11].

Postnatal investigations beside physical examination and ultrasonography (US) differs to some extent between centres according to the local standards, but may include voiding cysto-urethrography (VCUG), Technitium-mercapto-acetyltriglycine scintigraphy (MAG3) and dimercaptosuccinic acid scintigraphy (DMSA).

Typically, the first postnatal US will be delayed for 1 week to avoid false negative results during the period, when the baby is oliguric. Based on the results of the first US, the severity of the

hydronephrosis, bilateral abnormality and involvement of the ureters and bladder, follow-up is individualized.

Voiding cysto-urethrography is carried out, if VUR, bladder or urethral pathology are suspected. Whenever VUR is diagnosed a DMSA scan is undertaken to determine the differential function and any renal scarring.

Diuretic renograms are taken to diagnose obstructive uropathy defined as partial or no response to furosemide administration on MAG3.

Many studies have analysed outcome data on antenatally detected hydronephrosis as well as the results of the postnatal work-up, and the deviating results reflect a wide spectrum of study designs over a long period of time [2], [10], [11], [12], [13], [14]. More recent prospective studies find UPJO more common than VUR (40–45% vs. 30–33%) followed by PUV (7–13%) and vesico-ureteral junction obstruction (VUJO) (5–6%) [2], [11] (LoE 2b). Hitherto, obstructive uropathies seem to be more frequent than non-obstructive uropathies in neonatal hydronephrotic kidneys. However, another studies found hydronephrosis without other abnormalities to be the largest group identified at postnatal US [15], which may reflect different definitions of RPD and referral practices.

3.2 Risk factors for UTI with antenatal hydronephrosis

Children with AH are at increased risk of postnatal UTI [3]. Studies on the outcome of isolated AH have concluded that infants with mild renal pelvic dilatation only need clinical and ultrasound follow-up as the resolution rate is high and the risk of UTI is rather low [4], [8]. In the group of infants with normal postnatal US the incidence of UTI is 3.8% resembling that in the normal population [15], [16].

Since UTI is associated with significant morbidity and potential long-term medical problems, it seems essential to identify the infants with AH, that require special attention postnatally in terms of more investigations, closer follow-up, CAP or even surgery to reduce the risk of especially febrile UTI.

Ongoing uncertainty about the effectiveness of antibiotic prophylaxis for preventing UTI and concerns about long-term adverse effects of antibiotics have been raised, particularly related to the risk of bacterial resistance, which further emphasizes the need for consensus in this area.

The studies presenting results of the association between AH and risk factors for UTI are very heterogeneous. There are no randomized trials, some are prospective cohort studies and others are retrospective observational studies with obvious limitations due to study design. However, all recent studies show increased risk of febrile UTI with hydronephrosis, especially with high grade hydronephrosis and hydroureteronephrosis [15], [17], [18]. At the same time female gender, no antibiotic prophylaxis and uncircumcised boys often were shown to have a higher risk of catching a UTI early in life [17], [19], [20].

A Brazilian prospective study included 172 with AH, all on CAP if RPD >10 mm and/or VUR on VCUG. None were circumcised and the incidence of UTI was 14% (74% were on CAP) [17] (LoE 3). Analysis showed independent predictors of UTI to be female gender and clinically significant uropathy. Limitations of the study were uncertainty about the accurate incidence of UTI (method of urine sampling, timing of sampling, symptoms), compliance with CAP and a small number of events (UTI), which make interpretation of the results more difficult.

Lidefelt et al. conducted a small prospective study of 103 infants with AH and a postnatal follow-up, where those with RPD >15 mm and/or VUR grade III–V were kept on CAP. The number of significant uropathies in the group of abnormal postnatal US (n=50) were few, and only in infants with dilated VUR on CAP and in a single infant with megaureter, UTI was detected [15] (LoE 3). As it was a small study with a limited number of events and many hydronephrosis without other abnormalities the conclusion was not to recommend CAP in newborns with AH, who do not have nephrourological abnormalities or clinically significant VUR.

In a retrospective observational study 405 infants with AH referred to a tertiary centre for further follow-up were assigned to either a CAP group or a no CAP group and outcome on primarily febrile UTI as well as the circumcision status were noted. Independent risk factors for febrile UTI were ureteral dilatation, high-grade VUR and UVJO. More specifically, children with ureteral dilation >11 mm not maintained on CAP had a 5.54 fold increased risk of febrile UTI compared to those on CAP [19] (LoE 3). Interestingly, contrary to other studies the circumcision status did not have any impact on the risk of developing febrile UTI.

As the study group were infants referred to a tertiary center, they may represent a selected group of high risk cases not representative of the general population, which could have influenced the initial decision on circumcision and CAP status and hence the incidence of UTI.

A Canadian group published a number of studies on risk factors for febrile UTI [18], [20]. A retrospective database review of 376 infants with AH and risk factors such as high grade hydronephrosis, VUR, CAP and circumcision status showed that antibiotic prophylaxis was prescribed preferentially to females, those with high grade hydronephrosis and those with VUR [20] (LoE 3). Febrile UTI was detected in 13.3% and further analysis found high grade hydronephrosis, female gender and uncircumcised status in males to be independent risk factors for febrile UTI. Antibiotic prophylaxis was not associated to a reduced risk of febrile UTI in this study group. The relative low number of events (febrile UTI) and the uncertainty about the compliance with CAP may explain this surprising finding. So the researchers designed a prospective longitudinal study to further address those limitations [18] (LoE 2b). Data were collected on 334 patients and febrile UTI developed in 19%. Females and uncircumcised males with high grade hydronephrosis had significantly higher febrile UTI rates and thus may benefit from CAP, provided that patients with VUR were excluded from the study. Despite the well-designed study, the referral practise may result in a selected group of high grade hydronephrosis, which potentially bias the results.

3.3 Obstructive hydronephrosis/hydroureteronephrosis

Several studies have repeatedly shown hydroureteronephrosis to be associated with febrile UTI [5], [19], [21], [22], [23]. Especially, the infants with moderate to severe dilatation of the ureter (>11 mm) seem to be at risk. In this group of patients CAP and male circumcision are believed to reduce the incidence of febrile UTI and thus may prevent deterioration of kidney function. Often these prophylactic initiatives serve as temporary precautions in order to postpone surgery until the child is older.

A retrospective evaluation of 105 patients with severe hydronephrosis due to obstruction and no CAP showed a high incidence of febrile UTI (36.2%), especially before the age 6 months and in infants with lower ureteral obstruction compared to those with UPJO [21] (LoE 3). More than 70% underwent corrective surgery, when UTI or any other sign of worsening of the obstruction occurred. In the group followed without surgical intervention UTI developed in 42% leading to the recommendation, that infants with severe obstructive hydronephrosis should be treated with CAP at least for 6 months. The lack of control group, possible selection bias and small numbers of lower ureteral obstruction cases call for further prospective studies.

In 2008 the same institution published a larger retrospective study of 430 patients with non-refluxing hydronephrosis. A comparison of patients with vs without obstructive uropathy confirmed the high incidence of febrile UTI (39%) in neonates with obstructive uropathy and severe hydronephrosis or hydroureteronephrosis [5] (LoE 3).

In a small group of 49 children with 56 primary obstructive megaureters who was observed conservatively, UTI was the most common complication and turned out to be 55% lower in infants on CAP. Prophylaxis appeared particularly effective in the first 6 months of life, but even during the second year of life there still was a high incidence of UTI in an untreated group (0.46 UTI/year). Only 23% were treated surgically either primarily or after a period of observation with repeated renograms. Congenital kidney hypoplasia seemed to be more related to adverse outcome than the degree of obstruction and the rate of spontaneous resolution was about 50% [22] (LoE 3). Limitations of the study were the

retrospective approach, a heterogeneous group of patients (a mixture of AH and hydronephrosis incidentally detected later in life) and the relatively small number of patients. However, the authors concluded in keeping with other groups in terms of recommending CAP to infants with hydroureteronephrosis [5], [18], [19], [21].

The latest prospective study of the fate of primary non-refluxing megaureters looked into the risk factors for febrile UTI, indications for surgery and time to resolution [23] (LoE 2b). Similar to related studies the incidence of febrile UTI was 34% [5], [21]. As many as 76% of megaureters resolved during follow-up and a ureteral diameter of ≥ 17 mm was significantly associated with a higher rate of surgical intervention. Furthermore, circumcision (numbers-needed-to-treat, NNT was 4.5) and CAP (NNT was 3) significantly decreased the rate of febrile UTI. Again, interpretation of the results may be biased by referral bias, small number of certain subgroups of patients and a relative short follow-up.

In general, spontaneous resolution rates are high in cases with obstructive megaureter, CAP is recommended since the risk of febrile UTI is increased during the first 6 to 12 months of life and surgery is postponed, although the chance of having an operation varies widely (23–73%).

3.4 Circumcision in boys with urinary tract abnormalities

The risk of UTI in a boy with an anatomically normal urinary tract is 1%. Circumcision in a normal boy will reduce the risk of UTI by 90% [24]. In most cases, circumcision in boys is carried out for cultural or religious reasons, but it is also undertaken, because it is thought to improve hygiene and reduce the risk for certain diseases as well as UTI. Since the risk of UTI is increased in boys with complex abnormalities of the urinary tract, circumcision may turn out to be beneficial in chosen conditions [18], [20], [23]. Complication rates following circumcision vary between 2 and 10% [25], which must be taken into consideration when calculating the risk/benefit ratio for a particular group of patients.

A meta-analysis of published data on the effect of circumcision on the risk of UTI in boys has shown, that the number of normal boys who need to be circumcised to prevent one UTI is 111 [26] (LoE 1b). Furthermore, the risk of recurrence of UTI in boys with recurrent UTI and high grade VUR was 10% and 30% and the NNT were 11 and 4 respectively. Considering the risk of complications of male circumcision, the net clinical benefit is concluded acceptable in boys at high risk of UTI.

Recently, a review made a risk/benefit calculation of what evidence exists for circumcision in boys with abnormalities of the urinary tract (VUR, PUJO, VUJO and PUV) [27] (LoE 2b). The risk of UTI was significant in boys with VUR, VUJO and PUV resulting in a plausible protective effect of circumcision and an estimated NNT of 4, 3 and 2 respectively (Table 1).

Other studies on risk factors for febrile UTI in hydronephrosis and hydroureteronephrosis single out uncircumcised status as an independent risk factor in cases with high grade hydroureteronephrosis [18], [20], [23].

Table 1: Tabulation of UTI risk for abnormalities of the urinary tract in boys correlated with benefit from antibiotics, possible benefit from circumcision (plausible = projection from epidemiological studies of Wiswell et al.) [27].

Condition	Risk of UTI	Protective effect of antibiotic prophylaxis?	Protective effect of circumcision	Circumcisions NNT to prevent 1 UTI
VUR	30% [26]	In dilating reflux [29]	Plausible	Estimated 4

Condition	Risk of UTI	Protective effect of antibiotic prophylaxis?	Protective effect of circumcision	Circumcisions NNT to prevent 1 UTI
VUJO	40% [5]	Reduction incidence 50% [21]	Plausible	Estimated 3
PUJO	14% [5]	?	Plausible	Estimated 10
PUV	56% [28]	?	Retrospective case-note review [28]	2 [28]

The efficacy of circumcision in boys with PUV was documented in a retrospective cross-sectional case note review [28] (LoE 2b). Seventy-eight patients were identified and 27 were subsequently circumcised for religious reasons. The incidence of UTI was reduced by 83% after circumcision and further calculations showed, that every circumcision on average prevents 1 UTI.

Despite the lack of studies with focus on the association between male circumcision and the risk of UTI in specific urinary tract abnormalities, the existing studies on risk factors for UTI in hydronephrosis and PUV suggest that circumcision status may influence the incidence of UTI. Therefore, in high risk urinary tract abnormalities circumcision needs to be taken into consideration when counselling parents.

4 Further research

For the time being the association between UTI and obstructive uropathy is only explored to a limited extend. There is a need for detailed research on risk factors for UTI in congenital upper urinary tract obstruction with strict inclusion and exclusion criteria preferably in a randomized-controlled setting. Likewise, the benefits of CAP vs. circumcision in boys as well as the risk/benefit of an operation compared to CAP needs clarification. Long term follow-up on each modality (CAP, no CAP, surgery) will add further knowledge to the way we follow or treat the patients. Since many of the anomalies of interest are rare, a multicentre approach seems to be worth considering.

5 Conclusions

There is a wide variability in the management of upper urinary tract obstruction. Continuous antibiotic prophylaxis is typically prescribed postnatally, whenever hydronephrosis is diagnosed awaiting further diagnostic work-up, before deciding whether or not to continue the prophylaxis. Many studies have documented a high resolution rate and a low risk of UTI in mild hydronephrosis during the first year. The criteria for keeping the infant on CAP vary to some extent depending on the local cut-off levels for RPD, ureteric dilatation and VUR grade. Despite the heterogeneity of the studies, the relative low level of evidence, lack of randomized studies, small study populations and other study limitations, there seems to be a general finding of the need for CAP in infants with hydroureteronephrosis and possibly a benefit of male circumcision in the same group of patients. Whether CAP in this group of patients merely postpones surgery or maybe even precludes it, needs to be looked further into.

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