

Urinary tract infection in infants in spite of prenatal diagnosis of hydronephrosis

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Abstract. The efficacy of preventing neonatal urinary infection in infants by diagnosing hydronephrosis in the fetus on obstetrical ultrasonography was studied. 426 infants had urologic evaluation between 1984 and June 1991 because they had hydronephrosis detected in utero. Thirteen with posterior urethral valves were excluded. Of the remaining 413, 13 (3.1%) presented with urinary infection in the first 6 months of life. Ten of the 13 were boys and 7 were not circumcised. Eleven of the 13 infants less than 2 months old were formula-fed. The causes of hydronephrosis were reflux alone in 6, ureteropelvic junction obstruction in 6 (with coexisting ipsilateral reflux in 4), and primary megaureter in 1. Ultrasonography alone was insufficient to exclude reflux. Amoxicillin-resistant bacteria were the causative organisms in all 10 for whom bacteriology data was available. Four categories of management failure were identified: 1) failure of communication of the prenatal findings, 2) antibiotics not prescribed, 3) antibiotics prescribed but not administered, and 4) infection in spite of continuous antibiotic prophylaxis. Uncircumcised formula-fed male infants with reflux seemed to be at special risk for infection.

The detection of asymptomatic congenital hydronephrosis by maternal-fetal ultrasonography (US) has usually permitted not only early postnatal relief, by surgery, of significant urinary obstruction but also prevention of postnatal infection by administration of antibiotic prophylaxis. We have seen 13 infants presenting with urinary tract infection (UTI) in spite of the prenatal diagnosis of hydronephrosis. The purpose of this report is to analyze these cases to try to determine why their management failed.

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Patients and methods

From 1984 to June 1991, we have evaluated 426 infants in whom hydronephrosis was detected *in utero*. Thirteen of them, found to have posterior urethral valves, were excluded from this series since they had immediate postnatal management. Among the 413 remaining babies, 13 were prospectively identified who presented with UTI during their first 6 months of life. Their medical records and imaging studies, including prenatal (when available) and postnatal US, voiding cystourethrography (VCUG), excretory urography (EU), and renal scintigraphy, have been reviewed and form the basis for this report. Cyclic voiding cystourethrograms were performed in all patients [1].

Results (Table 1)

Thirteen of 413 infants (3.1%) presented with urinary infection in the first six months of life and 11 were one month old or less. Two patients had 2 infections. Ten were boys and 7 of these were not circumcised. Only 2 of the 13 infants less than 2 months old were breast-fed. Bacteriology results were available for 10 infections; urine and/or blood cultures grew *E. coli* in 4, *Staphylococcus* in 3, *Enterobacter* in 2, and *Klebsiella* in 1. All of the bacteria were "resistant"¹ *in vitro* to amoxicillin, the most commonly prescribed antibiotic in our hospital for this age group. The causes for hydronephrosis were vesicoureteral reflux alone in 6 (3 with the so-called megacystis-megaureter association (2)), ureteropelvic junction (UPJ) obstruction in 6 (with coexisting ipsilateral reflux in 4, mild in 3, and severe in 1), and primary megaureter in 1. All 13 infants eventually had surgical correction of their uropathy.

Four categories of management failure were identified. Representative patients are presented for each category.

Failure of communication

A male infant (patient # 2) was hospitalized on day 13 of life with fever and irritability. Culture of both urine and blood were positive for *Staphylococcus aureus*, resistant to amoxicillin. Prenatal US had detected an abnormality

¹ "resistance" is based on achievable serum antibiotic level

Table 1. UTI in spite of prenatal diagnosis of hydronephrosis

| Case # | Gender/Circumcision | Antibiotic Prophylaxis | Age at UTI | Problem | Bacterium | Diagnosis | Comments |
|--------|---------------------|------------------------|------------|-----------------------------------|--------------------------|---|---|
| 1 | ♂/no | no | 6 mo | Communication | – | Reflux (4), poor function | |
| 2 | ♂/yes | no | 13 d | Communication | <i>Staph. aureus</i> | Reflux (5), MC-MU, IRR | 16-year-old mother |
| 3 | ♂/yes | no | 18 d | Antibiotics not prescribed | <i>Staph. aureus</i> | UPJ, mild reflux, horseshoe kidney, pyohydronephrosis | Presented in 1984; mother had <i>Staph. pyodermitis</i> |
| 4 | ♀ | no | 17 d | Antibiotics not prescribed | – | Reflux (4), IRR | Incorrect pre- & postnatal diagnosis of UPJ obstruction |
| 5 | ♂/no | no | 21 d | Antibiotics not prescribed | – | UPJ, mild reflux | |
| 6 | ♂/no | no | 21 d | Antibiotics not prescribed | <i>Enterobacter</i> | Reflux (4) | Normal postnatal US |
| 7 | ♂/no | no | 11 d | Poor compliance | <i>E. coli</i> | UPJ, pyohydronephrosis | Spanish-speaking parents |
| 8 | ♂/yes | no | 23 d | Poor compliance | <i>E. coli</i> | Primary megaureter | Parents from Yugoslavia |
| 9 | ♂/no | yes | 9 d | Infection in spite of antibiotics | <i>Enterobacter</i> | Reflux (5), MC-MU, IRR | Two “breakthrough” infections on antibiotics |
| | | | 2 mo | Infection in spite of antibiotics | <i>Staph. not aureus</i> | | |
| 10 | ♀ | yes | 3 mo | Infection in spite of antibiotics | <i>Klebsiella</i> | UPJ, mild reflux | |
| 11 | ♀ | yes | 31 d | Infection in spite of antibiotics | <i>E. coli</i> | UPJ | |
| 12 | ♂/no | yes | 21 d | Infection in spite of antibiotics | – | Reflux (5), MC-MU | |
| 13 | ♂/no | yes | 1 mo | Infection in spite of antibiotics | <i>E. coli</i> | UPJ, severe reflux | Two “breakthrough” infections on antibiotics |

Notes: MC-MU = megacystis-megaureter; UPJ = ureteropelvic junction obstruction; IRR = intrarenal reflux; reflux = maximum grade on either side

of the “kidneys” according to his 16-year-old mother. This finding was unintentionally not communicated to the pediatrician and therefore antibiotic was not prescribed. Left grade 5 and right grade 4 reflux with bilateral intrarenal reflux, good drainage, a large smooth-walled bladder, and normal urethra, (the so-called megacystis-megaureter association [2]), was demonstrated by VCUG on day 21.

Antibiotic not prescribed

Prenatal US revealed left hydronephrosis in a female fetus (patient # 4) and this was confirmed by US postnatally. A dilated ureter was not seen on either study and the presumptive diagnosis of obstruction at the ureteropelvic junction was made, and therefore an antibiotic was not prescribed. She presented at 1 week of age with fever and was found to have UTI. VCUG showed bilateral reflux (left grade 4 with intrarenal reflux, right grade 3) with good drainage. There was no obstruction.

Antibiotic prescribed but not administered

A male infant (patient # 7) had the prenatal diagnosis of hydronephrosis. After delivery, a prophylactic antibiotic was prescribed and explanations were given to the Spanish-

speaking parents through an interpreter. Uroradiologic evaluation was scheduled. The prescription was never filled and at 11 days of age, he developed a febrile illness. Right pyohydronephrosis was shown by US. A percutaneous nephrostomy tube was placed and he was begun on intravenous antibiotics. *E. coli*, resistant to amoxicillin, was cultured from the urine. Nephrostography showed obstruction at the UPJ. VCUG was normal.

Infection in spite of continuous antibiotic prophylaxis

A male fetus (patient # 9) was shown to have intermittent right hydroureteronephrosis on prenatal US. There was a family history of reflux. After delivery, he was begun on oral antibiotic prophylaxis. He presented irritable and febrile on day 9 of life. *Enterobacter cloacae* (resistant to amoxicillin) was cultured from urine, blood, and cerebrospinal fluid. VCUG on day 21 revealed the so-called megacystis-megaureter association with *bilateral* grade 4–5 reflux, intrarenal reflux, and prompt drainage of the refluxed contrast agent. He was discharged on oral antibiotic prophylaxis (trimethoprim-sulfamethoxazole [TMP-SMX]). At age 2 months, he presented again with fever and irritability. *Staphylococcus* (not aureus or epidermidis) resistant to both amoxicillin and TMP-SMX was cultured from the urine.

Table 2. Causes of hydronephrosis in infants with urinary infection in spite of diagnosis of hydronephrosis prenatally

| 4 Main types of congenital hydronephrosis ^a | Total # of prenatal diagnoses and % of total | # and % with UTI |
|--|--|--|
| UPJ obstruction | 271 (65%) | isolated 2 (0.7%) + reflux ^b 4 (1.4%) (2.1%) |
| UVJ obstruction | 59 (14%) | 1 (1.7%) |
| Reflux ^b | 47 (11%) | 6 (12.7%) |
| Duplex system with upper pole hydronephrosis | 36 (9%) | 0 |
| Total | 413 | 13 |

^a Posterior urethral valves excluded ($n = 13$)

^b Thus 10 patients had either reflux alone or reflux coexisting with obstruction

Discussion

In the pre-ultrasound era, a common presentation for many children with congenital hydronephrosis due to obstruction or reflux was urosepsis in the first months of life [3]. One of the advantages of the prenatal diagnosis of hydronephrosis is that it offers the opportunity to prevent, by administration of prophylactic antibiotic [4], the initial episode of infection that may be more damaging to the kidney than the underlying congenital anomaly itself. In most cases, this seems to work well even though we have no way of knowing if those infants on antibiotic prophylaxis would have had UTI if they had not been treated. However, we have seen 13 patients out of 413 (3.1%) in 7 years in whom this approach was not successful. Ten of these 13 patients (77%) were male; the same male preponderance of urinary infection has been reported [3, 5] for all infants in the first 6 months of life (females predominate thereafter). Of the 10 boys, 7 were not circumcised; uncircumcised boys have more UTIs in infancy than their circumcised counterparts [6–11]. Of the 3 who were circumcised, none had received antibiotic prophylaxis. Approximately 60% of male infants in our area are circumcised. Nine of the 11 infants less than 2 months old with UTI were formula-fed; recent reports [12, 13] have suggested that breast feeding may protect against UTI in the infant.

Many of the cases reported here represent so-called “system failures”. Patients # 1 and # 2 are problems of communication. Prenatal imaging is unusual since often the radiologist receives the request for the examination from the obstetrician, but the results are more important for the pediatrician or pediatric urologist who may not even have been chosen yet.

In patients # 3–6, management failed (antibiotic was not prescribed) for different reasons. In patient # 3, born in 1984, the importance of antibiotic prophylaxis was not yet known and it was cases such as this that led to the routine use of antibiotic after delivery in infants with hydronephrosis, in order to prevent the first episode of infection. Now, antibiotic is routinely recommended to begin shortly after delivery and is continued until urologic evaluation defines the pathologic anatomy and physio-

logy so that a more precise treatment can be formulated [4]. Amoxicillin is most commonly used in our hospital because it has usually been effective against the common urinary pathogens. However, the frequency of strains of bacteria resistant to amoxicillin is increasing [14]. TMP-SMX and derivatives have not been preferred in the first week or two of life, especially in babies with jaundice, because their elimination competes with the elimination of bilirubin.

The non-specificity of prenatal US is shown by patients # 4 and # 6. US (pre- or postnatally) is especially insensitive to the presence and degree of reflux [15, 16]. The incorrect diagnosis of UPJ obstruction was made in patient # 4 and patient # 6 was thought to be normal, and so antibiotic was not prescribed for either infant. It is unusual for infants or children with uncomplicated UPJ obstruction to present with pyelonephritis. This happened in only 2 infants (0.7% of all UPJ obstructions in this series). A precise anatomical diagnosis should not be made on the basis of US alone, i. e., before VCUG is performed, for this can lead to withholding prophylactic antibiotic.

Patients # 7 and # 8 did not receive the antibiotic that was prescribed and illustrate the importance of making sure that the parents understand the rationale of the treatment and its importance. This is not an uncommon problem. In 11% of the families of all patients seen in our hospital, English is not the primary language spoken in the home.

Reflux, either alone or coexisting with obstruction seemed to predispose the infant to UTI since of the 13 patients in this series, 10 had reflux (Table 2). Six infants had isolated reflux and in only one was it uncomplicated. However, this one patient (# 6) had other possible risk factors for UTI, since he was uncircumcised, premature (born at 34 weeks gestation), and formula-fed. Of the other 5 with reflux alone, 1 had poor function of the affected kidney (# 1) and 1 had intrarenal reflux (# 4). Three had the megacystis-megaureter association with aberrant micturition [2] and considerable stasis of urine (# 2, # 9, and # 12). Six infants had UPJ obstruction (2.1% of the 271 infants with prenatally diagnosed UPJ obstruction) and 4 of the 6 had coexisting vesicoureteral reflux (3 mild, 1 severe). Although this association of reflux and obstruction has been described [17], it is uncommon and probably is yet another risk factor for UTI. Only 1 (# 8) of the 59 infants with primary megaureter and none of the 36 infants with a duplex collecting system and upper pole hydronephrosis detected by fetal US during the 7-year-period presented with infection in the first 6 months of life.

In summary, infants with UTI in spite of the prenatal diagnosis of hydronephrosis demonstrate the many potential pitfalls as regards diagnosis and treatment of such patients. Most can and do avoid the first episode of UTI that can be so damaging to the affected kidney. Infants with reflux who have retained their foreskin and who are being formula-fed may be at special risk. The problems of 1) infection by an organism that is resistant to the prophylactic antibiotic, and 2) the best antibiotic (including dose and frequency of administration) for prophylaxis, remain to be solved.

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Commentary

Vesico-ureteric reflux should be suspected in any infant with hydronephrosis detected on antenatal ultrasonography. With the current state of knowledge any degree of antenatal upper tract dilatation should lead to postnatal investigation. The published studies have reported that the natural history of vesico-ureteric reflux diagnosed following the detection of antenatal hydronephrosis is characterized by a male preponderance ranging from 2:1 to 5:1, a high grade of severity of reflux and, importantly, the fact that the resolution rate of reflux detected in this way is about 40% by the age of 2 years. There is also evidence that about one-fifth of refluxing kidneys which have been diagnosed following the detection of antenatal hydronephrosis, have decreased function on DMSA scanning. This is in the absence of urinary tract infection. Rather than showing areas of focal renal parenchymal scarring these kidneys are typically smooth and symmetrically reduced in size with no focal defects, more akin to the kidney damaged by obstructive uropathy. However in this institution, Anderson, Abbott and Mogridge (personal communication) have found a preponderance of girls and the pattern of renal damage has been both global and focal.

The study by Dacher and colleagues audits the failure to prevent a complicating urinary tract infection developing within 6 months of age in 10 boys and 3 girls with a prenatal diagnosis of hydronephrosis. The paper stresses the importance of good communication between clinicians and parents, the continual reinforcement of the potential risks, and close supervision of the antimicrobial prophylaxis prescribed for these infants. Attention to detail is clearly important. If reflux is suspected there is a

strong case for antimicrobial prophylaxis to be commenced as soon after birth as possible so as to prevent the child developing a complicating urinary tract infection, which may then contribute to focal renal damage in areas of intrarenal reflux.

Amox cillin was used for both curative and prophylactic regimens of treatment. For many years it has been known that a high incidence of urinary tract pathogens are resistant to amoxycillin making it a poor choice of antibiotic before the antibacterial sensitivity profile is known. In addition there are no good prospective studies showing that amoxycillin is a useful agent for prophylaxis. From a pharmacokinetic view point it is not a good choice. The choice of drugs to be used for long-term antimicrobial prophylaxis should be extrapolated from the prospective studies in sexually active women in which trimethoprim alone, co-trimoxazole (trimethoprim-sulphamethoxazole) and nitrofurantoin have been the most effective.

Infants born with antenatal hydronephrosis and subsequently shown to have a dilating form of vesico-ureteric reflux probably do not warrant immediate surgery, because of the high chance that the reflux will resolve spontaneously in a relatively short period of time. It seems logical for these neonates to be treated with low-dose antimicrobial prophylaxis during the period of follow-up and prior to a decision being made to undertake an anti-reflux procedure.

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Response from authors

Preventing postnatal urinary tract infection is one of the prime advantages of prenatal diagnosis of genitourinary abnormalities. Choosing a prophylactic regimen is therefore of great importance. In this series, only 3% of neonates developed a urinary tract infection. The fact that most occurred in the first month of life is also a critical fac-

tor. Those familiar with neonatal and pediatric practice realize that the usual medications used for adult prophylaxis such as sulfa-based medications and furadantoin derivatives are contraindicated during the immediate neonatal period. Therefore, amoxicillin, although not perfect, remains one of the most logical choices. In those neonates with both reflux and significant obstruction, early reconstruction may be logical.

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continued on p. 412