

Sex Differences in Childhood Urinary Tract Infection*

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Bergström, T. (1972). *Archives of Disease in Childhood*, **47**, 227. **Sex differences in childhood urinary tract infection.** Comparison of the clinical picture of nonobstructed urinary tract infection in boys and in girls over the age of 1 year revealed marked differences. The male infections were characterized by a high rate of 'atypical' bacterial aetiology, macroscopical haematuria, and normal temperature, as compared to the female ones. The proportion of patients getting recurrent infections during long-term follow-up was the same in the two sexes. The number of recurrences was, however, higher in the girls than in the boys. Radiological changes similar to postinfectious scar formation were found in 20% of the boys at their apparent first infection.

Male and female urinary tract infections (UTI) in childhood show some clinical differences. A greater proportion of male than of female infections appears during the first month of life (Smellie *et al.*, 1964; Stansfeld, 1966; Smallpeice, 1968). Males show a higher ratio of obstructive malformations (DeLuca, Fisher, and Swenson, 1963; Stansfeld, 1966), which, however, does not explain the early onset (Laplane and Etienne, 1968; Bergström *et al.*, 1971). Smallpeice (1966) noticed a sex difference in the frequency of haematuria in UTI and made a plea for the inclusion of sex incidence in reports both on clinical and experimental work. However, mixed materials are still used for conclusions regarding aetiology, radiology, and natural history of UTI as if the disease were identical in males and females. The aim of the present investigation is to examine the clinical features of urinary infections with onset between the ages of 1 and 16 years in males and to compare these data with those of a matched female material.

Material and Methods

During the period 1960–1966, 49 boys aged 1 to 16 years and living in the town of Göteborg appeared in the Children's Hospital with their apparent first UTI. Since the town has only one paediatric department and few private practitioners, the material can be considered as unselected.

Five patients were excluded because of anatomical defects (see the section on Radiology). The study group thus consists of 44 male patients. A female control group matched with regard to age at first infection has been chosen from consecutive cases.

History. A careful history with emphasis on earlier urinary infections was taken, and included an examination of the patient's records from the newborn period and from the well baby clinics.

Diagnostic procedures and criteria. 'Clean catch' specimens were used for urinary examinations. Urine was kept at +4 °C until quantitative culture. Check-up cultures were always preceded by omission of therapy for at least 60 hours. Leucocyte counts were made on unspun urine. Clinical and bacteriological methods have been described in detail in earlier reports from this department (Winberg *et al.*, 1963; Bergström *et al.*, 1967, 1968). BUN was determined at the index infection, renal concentrating capacity both at the onset and at check-up (Winberg, 1959a).

In symptomatic patients a bacterial count of 100,000 or more per ml urine was usually required for diagnosis. Leucocyte counts of ≥ 25 cells/mm³ in males and ≥ 50 cells/mm³ in females were considered abnormal (Lincoln and Winberg, 1964). In 10 boys the diagnosis was accepted though their colony counts were $< 100,000$ /ml. All 10 had leucocyturia and symptoms compatible with UTI. There was no balanitis. Renal concentrating capacity was determined in all 10 and found to be decreased in 6. At least 3 of these 10 boys received antibiotic treatment before the first samples were taken.

In asymptomatic recurrences two cultures were usually obtained before therapy.

Radiology. Intravenous pyelography (IVP) was performed in 40 out of 44 boys and in 30 out of 44 girls.

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Those patients not investigated had immediate clinical and bacteriological improvement after therapy, no recurrence, and normal renal concentrating capacity within three months after infection, thus obstructive abnormalities seem improbable in those cases. Micturition cystourethrography (MCU) was performed within two months of the index infection in 34 boys and in 16 girls. The difference between boys and girls in the number of radiologically investigated patients depends on the fact that boys were usually investigated at the first infection, whereas girls were not investigated until the first recurrence unless there were complications at the index infection such as prolonged symptoms or persistent leucocyturia.

Follow-up. The patients have been followed according to a schedule involving re-examination at 13 days, 1, 2, 3, and 12 months after the index infection. Further re-examinations and interviewing were performed at intervals of 2 to 3 years. At recurrences this follow-up schedule was started anew. The length of follow-up appears from Table I. Medical advice by the investigator has been easily available to the patients of this study and the patients have been examined whenever they have had symptoms.

TABLE I
Follow-up After First Infection

Years	No. of Patients	
	Males (44)	Female Controls (44)
2-3	44	44
3-4	35	38
4-5	19	34
5-6	12	24
6-7	6	12
7-8	3	10
8-9	2	3

Results

Clinical findings. The age distribution is shown in Fig. 1. The leading symptoms at the

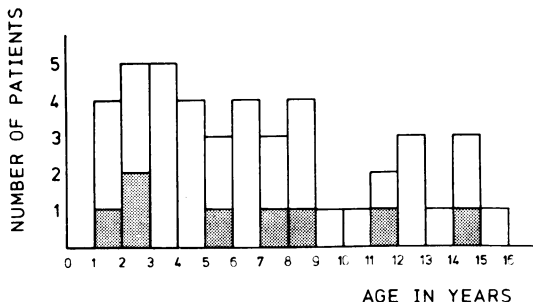


FIG. 1.—Age distribution of the 44 boys aged 1 to 16 years at their apparent first urinary infection.

▨ Parenchymal defects on IVP (see Radiology).

index infection appear from Table II. Fever was significantly more common in girls and haematuria in boys. Macroscopical haematuria was associated in 15 out of 19 boys with burning and frequency. It appeared in each patient only on one or two occasions and then became microscopic. It was not observed whether blood admixture was terminal or present in the whole urine portion.

TABLE II
Leading Symptoms at Index Infection

	Males	Female Controls	Significance of Difference
	44	44	
Fever ($\geq 38^\circ\text{C}$)	18	31	P < 0.01
Macroscopic haematuria	19	4	P < 0.001
Micturition symptoms	27	22	NS

Arterial hypertension was not seen during the index infections but a pressure of 150/110 mmHg together with a slight narrowing of the retinal arteries was seen during follow-up in one male patient. He had a reduction of the renal parenchyma at the first investigation. There was no renal artery stenosis.

Renal function. Blood urea nitrogen was below 20 mg/100 ml in all male and female patients. The concentrating capacity was temporarily decreased in 14 out of 16 febrile and in 10 out of 22 afebrile boys (Fig. 2). There was no sex difference. All 8 infections (5 male, 3 female) caused by staphylococci were associated with a transitorily decreased concentrating capacity.

Bacteriology. The bacterial aetiology and its relation to symptomatology at the index infection is presented in Table III. In the male group proteus infections were seen below the age of 10, and 4 of the 5 male staphylococcal infections above the age of 11. The sex difference in bacterial aetiology did not seem to explain the male and female difference in frequency of haematuria and fever.

Radiology. Out of the original 49 boys, 5 were excluded: 3 with unilateral hydronephrosis caused in 1 case by an aberrant vessel and in 2 by ureteral obstruction of unknown origin; 1 with a bladder stone and 1 with a bladder diverticulum without other abnormalities. One girl had unilateral hydronephrosis due to stenosis at the pelviureteral junction, and was excluded, as well as

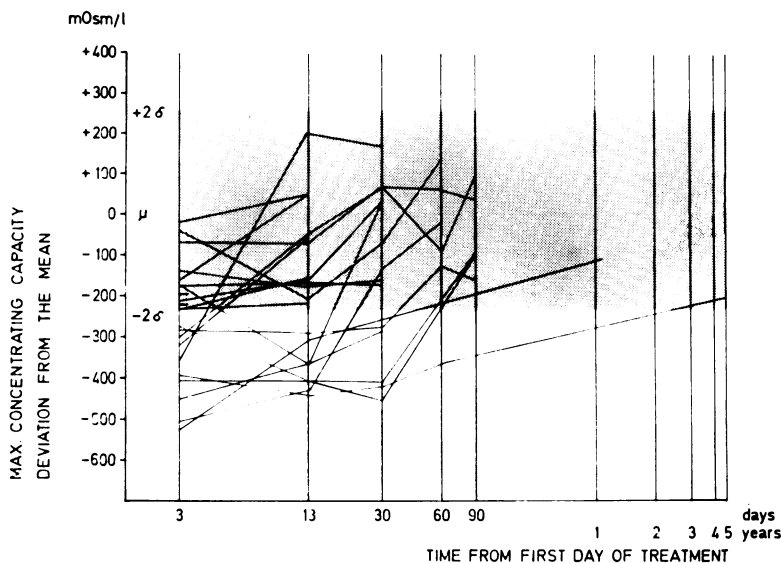


FIG. 2.—Renal concentrating capacity in 22 boys with afebrile infections. The concentrating ability in each examination is expressed as the difference between normal mean and measured value. Shaded area indicates mean \pm 2 SD in children without infection or obstruction (Winberg, 1959a).

the 4 matched female controls of the excluded boys.

The radiological findings in the rest of the group and in the female controls are shown in Table IV (see also Fig. 1). Blunting or clubbing of the calyces corresponding to a defect of the renal outline, resulting in a parenchymal narrowing, was present in 8 boys already at the apparent first infection. Blunting or clubbing without other detectable defects were seen in 3. Similar abnormalities were found at a significantly lower rate in the females.

There was a progression of the renal defects in one boy with parenchymal narrowing at the first known infection. In 2 of the 3 boys showing only clubbing of the calyces at the initial investigation

there was a defect of the renal outline as well at follow-up. These 3 patients with progressive changes had had only one recurrence each. None developed renal insufficiency. Details of the radiological follow-up will be presented later.

The radiological findings in the males were compared to the infantile history by scrutinizing the patients' records from the maternity hospital and from the Child Health Centres. Such data were available in all. Out of the 11 boys with parenchymal defects, 2 had a weight loss of more than 10% during the neonatal period and 2 others gained poorly in weight. There was no overt explanation for these abnormalities. Urine examinations had not been performed. The weight

TABLE III
Relation Between Bacterial Aetiology and Leading Symptoms at Index Infections

	Total		Fever		Micturition Symptoms		Macroscopical Haematuria	
	Males	Female Controls	Males	Female Controls	Males	Female Controls	Males	Female Controls
<i>Esch. coli</i>	15	39	4	27	9	21	8	4
<i>Proteus</i>	14	0	4	0	10	0	5	0
<i>Staph. albus</i>	5	3	2	2	4	0	2	0
Enterococci	2	1	2	1	0	0	0	0
<i>Klebsiella</i> , <i>Pseudomonas</i> , and different mixed infections	4	1	2	1	3	1	2	0
Unknown	4	0	4	0	1	0	2	0

TABLE IV

*Excretion Pyelography and Micturition Cystourethrography at First Infection**

IVP	Males	Female Controls	Significance of Difference
Number investigated	40	30	
Defect renal outline + calyceal blunting or clubbing	8‡	1	P < 0.05†
Calyceal blunting or clubbing only	3‡	3	—
MCU	Males	Female Controls	
Number investigated	34	16	
Vesico-ureteric reflux	6	6	NS

*Patients with obstruction and their matched controls excluded.

†Due to small numbers a randomized test according to Fisher-Irwin was used. The difference was found to be significant at the 5% level with a probability 0.58. Without randomization the difference was significant at the 8% level.

‡Progression seen in 3 out of these 11. (Ages are in Fig. 1.)

course was uneventful in the 29 patients with normal IVP.

Follow-up. Recurrences were seen in 14 males during the follow-up period shown in Table I. In 35 boys and 38 girls followed for a comparable time (3.8 years) there were 22 recurrences in 13 males, and 47 in 16 females. Fig. 3 suggests that the liability to get recurrence was highest in the first year after the index infection, but that it persisted for many years in some patients. A similar trend was found in the females. Most

recurrences in the males were reinfections. The recurrences like the index infections had a more varied aetiology in the males. Thus, only 7 out of 30 were caused by *Esch. coli* as compared to 47/52 in the females. Enterococci caused 13 male recurrences and 5 female. *Proteus* was seen in 4 male recurrences and in no female. In 9 boys with proteus infections check-up cultures showed insignificant numbers of proteus bacteria suggesting their presence in the urethral or preputial flora. There were no similar findings of proteus after *Esch. coli* infections.

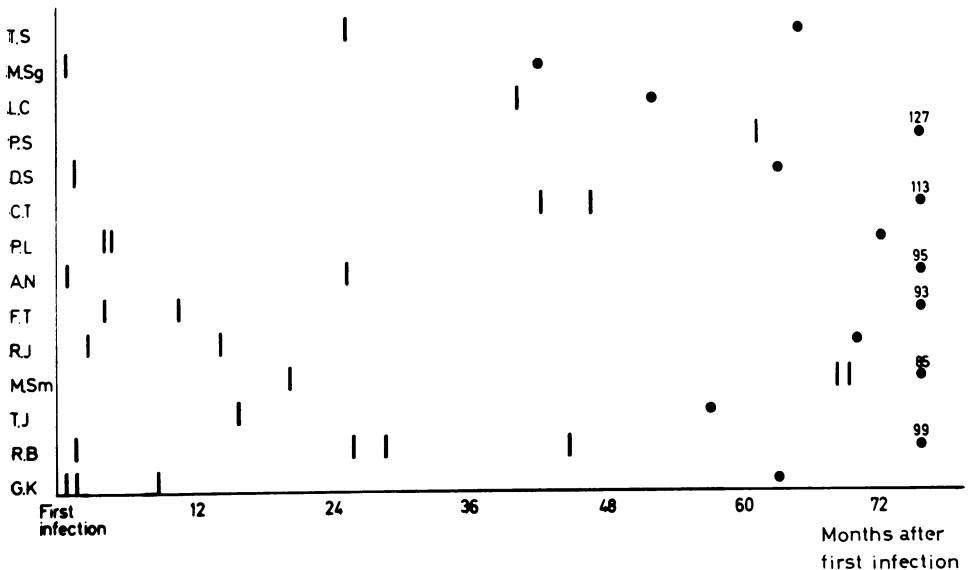


FIG. 3.—Appearance of recurrences in 14 boys. Probably iatrogenic infections were omitted.

| Recurrence.

● Last check-up. Months after index infection indicated.

Discussion

This investigation has disclosed four major differences between male and female subjects in respect of apparent first urinary infection appearing in children after the age of 1 year. Two-thirds of the male infections were caused by bacteria other than *Esch. coli*, as compared to 1/10 in the girls; haematuria, renal parenchymal defects, and afebrile infections were significantly more common in the males. The more frequent occurrence of haematuria has been pointed out earlier (Smallpeice, 1966, 1968).

Fifteen male infections were caused by proteus as compared to none in the female controls. In an earlier study proteus was found once in 237 females, 162 of whom were above 1 year (Bergström *et al.*, 1968). Since the male/female ratio of apparent first infection in ages above 1 year is about 1/7 in our material (unpublished), even the absolute number of proteus infections is higher in the male than in the female. The reason for this can only be a matter of speculation. Proteus may be present in the distal part of the male urethra more often than in the female. Existing data seem insufficient to evaluate this possibility (Kienitz, 1966). In a preliminary study we found that only 2 of 39 healthy boys had proteus in the distal urethra (K. Lincoln and T. Bergström, unpublished). Another possibility is that males susceptible to urinary infection have a urethral flora different from that in males not susceptible to urinary infections. The presence of a small number of proteus bacteria in the urine, probably of urethral origin following proteus infections may support the latter alternative. In these instances bacteria may also have resided in the prostatic ducts between infections, as shown by Meares and Stamey (1968). The role which the newly demonstrated antibacterial substance in the prostatic fluid (Stamey *et al.*, 1968) may play in the different bacterial aetiology in males is uncertain.

Obstructions and other abnormalities of the urinary tract are thought to favour infection with proteus (Tomaschoff, 1969) and other 'atypical' bacteria (de Wardener, 1967; Smallpeice, 1968). Since bacteria of these kinds are characteristic of male infections, even in the absence of obstruction, it is possible that this high frequency in obstructive infections is related more to sex than to obstruction.

The finding of a high rate of haematuria in boys is in accordance with the reports of Smallpeice (1966). Haematuria was in our cases not related to the infecting organism. The source of bleeding is obscure but the fact that 15 out of 19 boys with haematuria complained of burning and/or fre-

quency might suggest that the origin was situated in the bladder or the urethra. It should, however, be pointed out that in experimental pyelonephritis bleeding can be a common finding, probably due to ruptures of calyceal fornices (Heptinstall, 1964).

The most interesting finding in this investigation was the parenchymal defects revealed by excretion urography in 20% of the boys already at their apparent first infection. Such defects might be congenital due to dysplasia or vascular abnormalities, or acquired, caused by back pressure or infection. In one instance, a boy with a marked reflux, the lesions were similar to those described as typical of 'back pressure kidney' (Hodson and Craven, 1966). Congenital dysplasia of the renal parenchyma is usually associated with other anomalies, often causing obstruction of the urinary flow (Heptinstall, 1966; Bernstein, 1971), and thus seems less probable in the present cases devoid of obstruction. A renal biopsy performed in one boy did not show structural changes consistent with a diagnosis of renal dysplasia as defined by Bernstein (1968).

The lesions in our patients fulfil the radiological characteristics of 'chronic pyelonephritis' or post-infectious scar formation, as defined by Hodson (1959) and Hodson and Wilson (1965). This interpretation is further supported by the fact that progression was observed in three patients. The histological findings in the above-mentioned biopsy were also compatible with postinfectious scarring. Furthermore, renal dysplasia has not—as far as known by the author—been shown to be associated with the focal postinfectious scar as defined by Hodson (1959). It is well known that UTI are much more common in boys than in girls during the neonatal period (Lincoln and Winberg, 1964; Laplane and Etienne, 1968; Bergström *et al.*, 1971) and also that there is a male preponderance during the first few months of life (Stansfeld, 1966; Smallpeice, 1968). Since these infections often seem to pass unrecognized it is a reasonable hypothesis that the parenchymal reduction of our patients was the result of early infantile, undiscovered, and untreated infections. This might be reinforced by the finding that in 4 out of 11 boys with radiological defects a neonatal history consistent with UTI was found as compared to none in the 29 patients without radiological abnormalities.

The high rate of afebrile infections in males was not explained by the difference in bacterial aetiology. While fever usually is a sign of renal involvement (Winberg, 1959b; Stamey, Govan, and Palmer, 1965; Andersen *et al.*, 1965), afebrility might be consistent with infection confined either to the lower

urinary tract or to the renal parenchyma. A transitory lowering of the concentrating capacity in 10/22 boys suggests renal involvement in some afebrile infections. The difference in frequency of febrile infections in males and females is thus not entirely explained by difference in localization of the infection.

The proportion of boys and girls getting recurrent urinary infections during the long-term follow-up was about the same, but the number of recurrences *per capita* was much greater in girls. Thus one might get the impression that the disease has a better prognosis in boys than in girls when in fact scarring might be more frequent in boys than in girls.

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