INVITED ARTICLE

Recent Advances in the Treatment of Non-obstructive Urinary Tract Infection in Infants and Children

by

FRIEDRICH MANZ and OTTO MEHLS *

(From the Department of Nephrology, University Children's Hospital Heidelberg, Germany)

Abstract

In infants and children urinary tract infections are common and recurrent. For the first urinary tract infection elimination of bacteriuria with chemotherapeutic drugs is usually simple and effective. The long-term treatment of patients with urinary tract infection should reflect the individual risk to develop renal damage. Therefore, individual therapy must be picked out of several therapeutic schedules: Observation without chemotherapy, chemotherapy of active urinary tract infection, chemotherapeutic propiylaxis, suppressive chemotherapy and surgery.

* Presented at the Vth National Pediatric Congress, Medan, 14 — 18 June, 1981. Received 15th February 1982.

Introduction

Urinary tract infection is the second commonest bacterial infection in human. It is recurrent, may indicate unsuspected urinary tract malformation or obstruction and result in renal damage. The basis of the diagnosis is significant bacteriuria (in two midstream urine specimens more than 10^5 organisms/ml; in urine obtained by urethral catheterization more than 50000 organisms/ml, if the child is less than 3 years old, or more than 5000 organisms/ml, if the child is more than 3 years old; in urine collected by suprapubic aspiration any organism present in the culture media is regarded as significant).

Pathologic leucocyturia (more than 50 leucocytes/mm^3 in girls and male infants, more than 10 leucocytes/mm^3 in boys with an age more than 3 years) and pathologic erythrocyturia (more than 10 erythrocytes/mm^3) are additional diagnostic tools (Olbing, 1981).

Once the diagnosis is established active urinary tract infection has to be treated. Now in a second diagnostic step the risk of a patient to develop renal damage will be identified. Several diagnostic tools are helpful. The longterm treatment is based on the estimation of the individual risk of a patient to develop renal damage. Individual therapy must be picked out of several therapeutic schedules: observation without chemotherapy, chemotherapy of active urinary tract infection, chemotherapeutic prophylaxis, suppressive chemotherapy or surgery.

Treatment of the first urinary tract infection

If the patient shows no signs of upper urinary tract infection we start treatment with the appropriate drug, when the organism and the drug sensitivity is known. If the patient presents clinical symptoms of upper urinary tract infection, we perform suprapubic urine aspiration and start chemotherapy with the drug of first choice without delay. In oral chemotherapy the drug of first choice is co-trimoxazol, the combination of trimethoprim and sulfamethoxazol, as listed in Table 1. This drug is absorbed in the upper small intestine. Most pathogen organisms are sensitive and the sensitivity pattern of the intestinal bacteriae is not influenced. The drugs of second choice are cephalexin, ampicillin, amoxicillin, sulfonamides, nitrofurantoin and nalidixic acid. The dosage used in our department for cephalexin, ampicillin and amoxicillin are rather high.

Norman and Smellie (1977) used half of our dosages. In parenteral therapy the choice of the drug is based on the sensitivity of the patnogenetic organism. In recent years there has been great discussion about the adequate duration of treatment in urinary tract infection. Newborns should be treated for 14 days as urinary tract infection is usually associated with sepsis.

Urinary tract infection with clinical symptoms of upper urinary tract infection should be treated for 7 days.

In cystourethritis the adequate duration of treatment is controversial. Källenius and Winberg (1979) showed elimination of bacteriuria with a single oral dose of 200 mg sulfafurazol/kg in 27 of 29 girls, who showed bacteriuria sensitive to sulfonamide. Despite this and other results mainly in women, we think that it is too early to advise a single oral dose as a standard treatment (Kunin, 1981). Whether a chemotherapy lasting 3 or 4 days is adequate is also unknown. We, therefore, treat our patients with cystourethritis still for 7 days.

Chemotherapy is supported by instructions to the child. All patients should have a high fluid intake, frequent and complete voiding of the bladder and no constipation.

In girls we recommend further an adequate wiping technique, treatment of vulvitis, no tight trousers and no bathing in cold water for longer than 10 minutes.

Risks and risk factors in children with urinary tract infection

In children with urinary tract infection we fear persistance, recurrence and spreading of infection, renal damage, urolithiasis and hypertension.

Prevention of renal damage therefore is the most important aim of long-term treatment of urinary tract infection.

In the last decade a lot of work has been done concerning the pathogenesis of renal damage in patients with urinary tract infection in order to identify groups of patients with a high risk to develop renal damage. Based on these results the uniformity of the treatment of "chronic pyelonephritis" has been detached by several schedules for the long-term treatment of urinary tract infection reflecting the different risks to develop renal damage.

Risk factors for the development of progressive renal damage in urinary infection are listed in table 2. Vesicoureteric reflux and renal scarring have been observed in 12% of family members of patients with reflux nephropathy (Heale et al., 1979). In families, where the index patient had renal failure, the incidence of vesico-ureteric reflux and renal scarring was even more frequent (40%), suggesting an inherited basis for this disease (Bailey, 1979). But there is no uniform pattern of inheritance. Recurrent urinary tract infection and symptomatic urinary tract infection in the past are further risk factors.

The risk to develop renal damage varies with age and sex. The risk is highest in male infants and lowest in female pupils (Winberg et al., 1975). Enuresis, vulvitis and urinary tract infection are correlated. Several syndromes show a high incidence of urinary tract infection (Olbing, 1975): Atresia of anus, rectum or oesophagus, congenital heart diseases (atrial septal defect, ventricular septal defect), congenital megacolon, congenital scoliosis, chromosomal syndromes (L, D, E, 21, XO), embryopathies due to alcohol or rubella, epispadia, Fanconi anemia, hypospadia, oligodactylia, spina bifida, thoracic dystrophy and the syndromes of Allemann, Apert, Ehlers-Danlos, Klippel-Feil, Lesch-Nyhan, Marfan,

TABLE 1 : *Chemotherapy of active urinary tract infection*

	mg/kg/d	doses/d
Oral therapy		
First choice		
Co-trimoxazol (TMP/SMZ)	5/25	2
Second choice		
Cephalexin	100	3 — 4
Ampicillin	100	3 — 4
Amoxicillin	50	3 — 4
Sulfonamides	100 — 125	3
(Sulfadimidine, Sulfafurazole)		
Nitrofurantoin	5	3 — 4
Nalidixic acid	60	3 — 4
Parenteral therapy		
Aminoglycoside	2 — 4	3
Azlocillin	75	4
Carbenicillin	300	4

TABLE 2 : *Risk factors for the development of progressive renal damage in urinary tract infection (risk increased ↑, risk decreased ↓)*

I. Anamnesis : Urinary tract infection and reflux in relatives ↑. In the past: no urinary tract infection ↓ recurrent urinary tract infection ↑ symptomatic urinary tract infection ↑

II. Clinical status : Age: Infants ↑, 1 — 4 years ↑, > 4 years ↓ Sex: Male ↑, Female ↓ Syndromes ↑. :

III. Bacteriology : Atypical organisms ↑, adherence of bacteria to uro-epithelium ↑.

IV. Localization of urinary tract infection : Upper urinary tract infection ↑ Cystourethritis ↓, Asymptomatic bacteriuria ↓

V. Renal function : Acute decrease of glomerular filtration rate ↑, Acute decrease of renal concentrating capacity ↑.

VI. Renal morphology : Renal scarring ↑

VII. Urinary tract : Anomalies without obstruction ↑, Obstruction ↑, Urolithiasis ↑, Vesicoureteric reflux ↑.

Mayer-von-Rokitansky-Küster, Prune-Belly, Rubinstein-Taybi and Russell-Sliver.

Bacteriuria of an atypical organism is indicative of special problems. Recently Hanson et al. (1975) showed that girls with recurrent UTI may have an increased adherence of bacteria to the uroepithelium.

Urinary tract infection must involve the upper urinary tract to cause renal damage. Therefore, localization of urinary tract infection is of high diagnostic value. Culture of organisms from renal parenchyma or selective urine collection of an ureter are direct, but rare diagnostic procedures.

Other diagnostic methods give only indirect evidence of renal involvement in active urinary tract infection.

Fever and loin pains are good clinical indications in older children. Proteinuria, white blood cell casts in urine, leucocytosis, increased sedimentation rate and increased C-reactive protein are simple laboratory tests.

In research studies bladder washout technique, antibody coating of bacteriae, increased urinary isoenzyme excretion or an increase of specific serum antibodies against bacterial antigen or Tam horsefall protein may be helpful.

Impairment of renal function as shown by an acute decrease of glomerular filtration rate or a transitory decrease of renal concentrating ability is strong indirect evidence of the involvement of renal parenchyma (Berg, 1981).

The measurement of split renal function is a useful diagnostic tool especially for the diagnosis and follow up of unilateral or asymmetric renal damage. Klare et al. (1980) correlated kidney length, split effective renal plasma flow and split glomerular filtration rate. In unilateral vesicoureteric reflux grade 3 or more kidney length of the diseased kidney was 80% of the size of a normal kidney, whereas split effective renal plasma flow was 36% and split glomerular filtration rate was 44% of the function of a normal kidney.

Apparently kidney size in refluxing patients is not a good index for function, since kidney size is not diminished adequately due to the pelvicalyceal dilatation.

In morphology permanent renal damage in urinary tract infection is represented by chronic atrophic pyelonephritis or in excretory urography by renal scarring. Hodson (1979) defined renal scarring as an overall reduction in renal size, deformation of calyces and an indentation of the renal surface opposite to the deformed calyx (Fig. 1). The scars are usually situated in the polar regions. Vesicoureteric reflux, urinary tract infection and anomaly of the papillae are the main pathogenetic factors which induce renal scarring.

In order to recognize deformed kidneys the radiological kidney size of normal children must be known. Unfortunately the correlation of kidney length to body height, published by Hodson et al.

(1962), spread the standard deviation much too widely due to a statistical error. Therefore, radiological kidney size in normal children was defined recently by several authors (Chiaesson et al., 1981; Eklöf and Ringertz, 1976; Hodson, 1979; Klare et al., 1980). Klare et al. (1980) recommended for practical purpose the right (left) kidney length to body height or lumbar segment L_1 — L_4 (Fig. 2). Other measurements of kidney size are the quotient of the right kidney length to the left kidney length, the quotient of the upper parenchymal thickness to the lower parenchymal thickness or bipolar thickness (upper parenchymal thickness + lower parenchymal thickness) to body height.

Each disturbance of urinary transport is a risk for the development of renal damage. The frequency of anomalies of the urinary tract other than obstruction (e.g. duplication) is about 10 times greater in infants and children with urinary tract infection than in the general population, as Winberg et al. (1974) pointed out. Obstruction and urolithiasis are both important risk factors.

Vesico-ureteric reflux is common in infants and children with urinary tract infection. In newborns and infants with urinary tract infection about 50% show vesico-ureteric reflux (Winberg et al., 1974). Most of these refluxes disappear spontaneously. Classification of vesico-ureteric reflux according to Heikel and Parkkulainen (1966) is helpful in deciding whether to use primarily conservative management or surgical treatment (Fig. 3). Reflux grade I affects only the lower part of the ureter. In reflux grade II urine goes up to the pelvis. In reflux grade III ureter and pelvis are dilated. In reflux grade IV the calyces are dilated too, but there is still a bay due to the top of the papilla. On reflux grade V the whole upper urinary tract is dilated and all calyces are deformed. Primary conservative management is adequate for children with reflux grade I and II, whereas primary surgical management is prefered in reflux grade V.

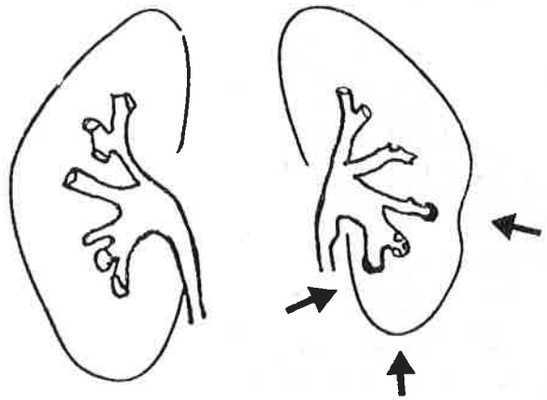
For reflux grades III and IV it is unknown whether conservative or surgical management give the better results (Report of the international reflux study committee, 1981).

Vesico-ureteric reflux is frequently associated with pathologic ureteric orifice configuration and scarring. In 208 children with urinary tract infection and 308 refluxing and 115 non refluxing ureters a normal ureteric orifice was associated with reflux in 26% of cases and with scarring of the corresponding kidney in 5% (Stephens, 1979).

A stadium like ureteric orifice showed reflux in 60% and renal scarring in 5%. If the ureteric orifice looked like a horseshoe reflux was observed in 78% of the cases and renal scarring in 33%. If it looked like a golfhole the incidence of reflux was 100% and that of scarring 81%.

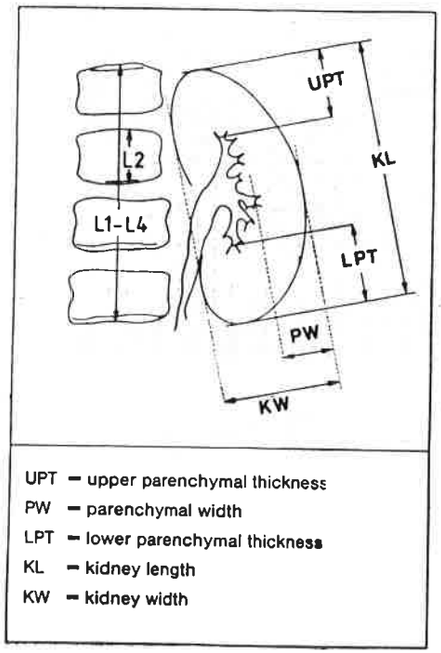
In summary, patients with urinary tract infection show an increased risk to

FIG. 1 : *Renal Scarring*



Overall reduction in renal size, deformation of the calyces, indentation of the surface

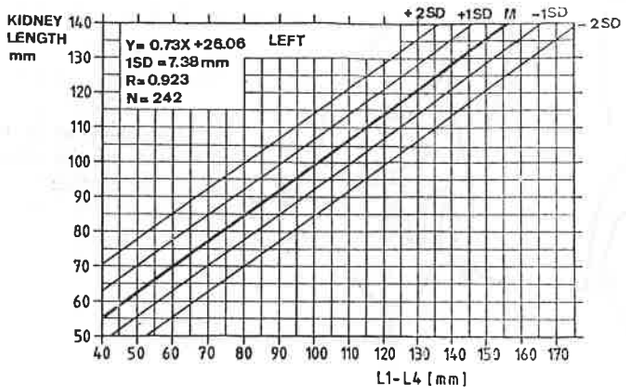
FIG. 2 : Measurements of kidney size

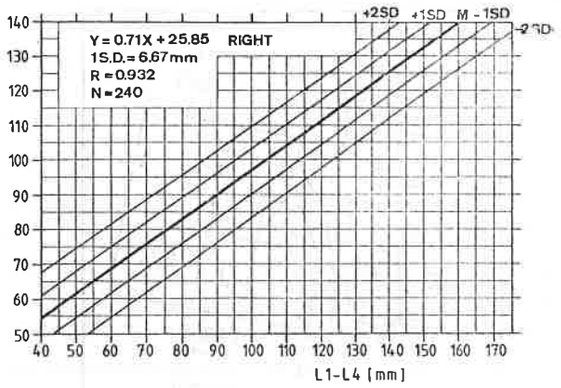


Radiological kidney size in children without kidney disease*

* B. Klare, B. Geiselhardt, H. Wesch, K. Schärer, H. Immich, E. Willich
Pediatric Radiology, Vol. 9, No 3 (1980)

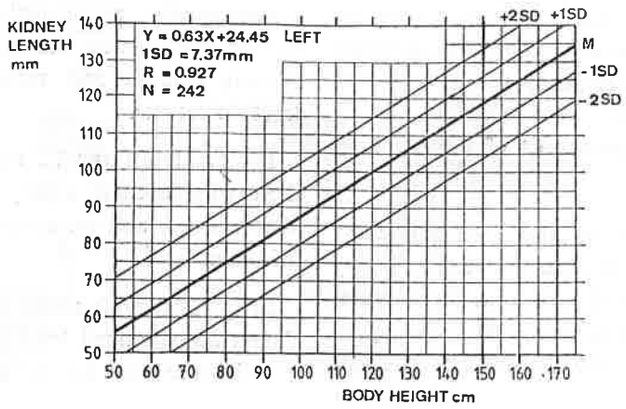
Relation between kidney length and lumbar segment (L_1–L_4)

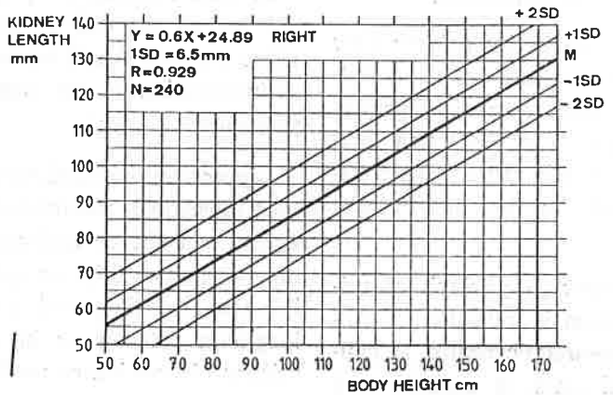




Quotient right kidney length/left kidney length
(indepedent of body height) = 0.973 (± 2SD: 0.881–1.065)

Relation between kidney length and body height





Quotient right kidney length/left kidney length
(indepedent of body height) = 0.973 (± 2SD: 0.881–1.065)

develop progressive renal damage, if they show recurrent symptomatic urinary tract infection and if there are disturbances of urinary transport including vesico-ureteric reflux.

Long term treatment of urinary tract infection

Observation without chemotherapy may perhaps be possible in the highly selected group of girls with asymptomatic bacteriuria (Kunin, 1981; Olling et al., 1981). But the therapeutic experiences in this group of patients is too short to give valid recommendations.

Chemotherapy of active urinary tract infection is indicated in infants and children with few recurrence of oligosymptomatic urinary tract infection and without vesico-ureteric reflux. The treatment corresponds to the first urinary tract infection.

Chemotherapeutic prophylaxis of urinary tract infection is indicated in children with vesico-ureteric reflux, in children with renal scars, in children with frequent recurrence of urinary tract infection (4 reinfections within 12 months) and in some children with symptomatic cystourethritis (Smellie et al., 1978; Smellie, 1981). The treatment is based on chemotherapy and instructions.

Co-trimoxazol and nitrofurantoine are the drugs of the first choice (Table 3). They were given in a single low oral dose in the evening. Drugs of second choice are nalidixic acid, sulfonamides and methenamine hippurate. The chemotherapeutic prophylaxis should be carried out for 6 months in children with normal kidneys and recurrent urinary tract infections.

It should last for 12 months in children with normal kidneys with minor abnormalities and recurrent urinary tract infection.

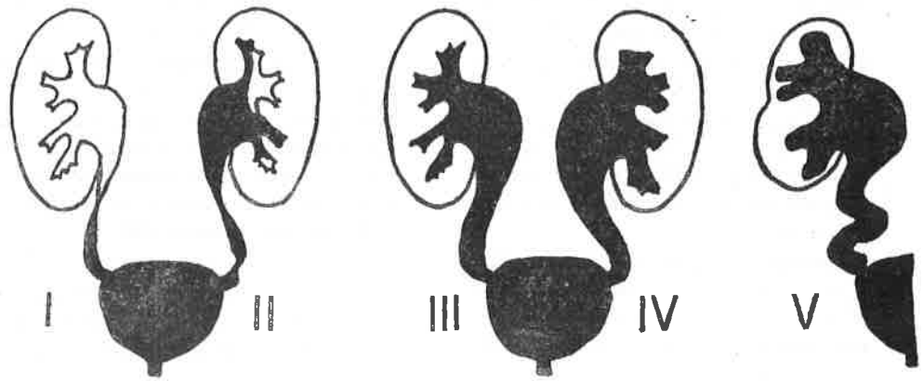
In children with reflux this treatment should be continued for 12 months after the disappearance of the reflux.

In renal scarring the prophylaxis should last to the end of kidney growth. Urine controls should be imposed without interruption of the chemotherapeutic prophylaxis.

Suppressive chemotherapy of urinary tract infection is recommended, if the infection can not be eradicated. This therapy suppresses only the spreading of the infection. It is indicated in children with long-term catheter or in children with urinary obstruction or urolithiasis before surgery or where surgery cannot be done.

Surgery should be considered in cases of obstruction and urolithiasis. Children with reflux should undergo an operation if they show vesico-ureteric reflux grade V, perhaps grade III and IV, if they have recurrent urinary tract infection despite chemotherapeutic prophylaxis or if there are side effects or non compliance of chemotherapeutic prophylaxis.

FIG. 3 : *Classification of vesicoureteric reflux in children. Heikel, P.E. and Parkkulainen, K.V.: Ann. Radiol. 9, 37 (1966).*



I. Reflux into the lower part of ureter
II. Reflux into a pelvis of normal size
III. Reflux into a dilated ureter and pelvis
IV. Reflux into a dilated ureter, pelvis and calyces. Single calyces may be deformed
V. Reflux into a dilated ureter, pelvis and calyces with deformation of all calyces

TABLE 3 : *Chemotherapeutic prophylaxis in urinary tract infections in children*

Treatment Instructions	mg/kg/d	doses/d
Chemotherapy		
Co-trimoxazol (TMP/SMZ)	1/5 (2/10)	1
Nitrofurantoine	1 (2)	1
Nalidixic acid	15 — 20	2
Sulfonamides	20 — 25	2
Methenamine hippurate	20 — 30	2

REFERENCES

1. BAILEY, R.R. : An overview of reflux nephropathy; in Hodson, J., Kincaid-Smith, P., Reflux nephropathy. p. 3 (Masson, New York 1979).
2. BERG, U. : Renal function in acute febrile urinary tract infection in children: Pathophysiologic aspects on the reduced concentrating capacity. Kidney int. 20 : 753 (1981).
3. CLAESSON, I.; JACOBSON, B.; OLSSON, T.; RINGERTZ, M. : Assessment of renal parenchymal thickness in normal children. Acta radiol. (Diag.) 22 : 305 (1981).
4. EKLÖF, O.; RINGERITZ, H. : Kidney size in children. A method of assessment. Acta radiol. (Diag.) 17 : 617 (1976).
5. HANSON, L.A.; AHLSTEDT,S.; JODAL, U.; KAIJSER, B.; LARSSON, P.; LIDIN-JANSON, G.; LINCOLN, K.; LINDBERG, U.; MATTSBY, I.; OLLING S.; PETERSON, H.; SOHL, A. : The host-parasite relationship in urinary tract infections. Kidney int. 8:28 (1975).
6. HEALE, W.F.; SHANNON, F.T.; UTLEY, W.L.F.; ROLLESTON, G.L. : Familial and hereditary reflux nephropathy; in Hodson, J., Kincaid-Smith, P., Reflux nephropathy. p. 48 (Masson, New York 1979).
7. HEIKEL, P.E.; PARKKULAINEN, K.-V. : Vesico-ureteric-reflux in children. Ann. Radiol. 9 : 37 (1966).
8. HODSON, C.J.; DREWE, J.A.; KARN, M.N.; KING, A. : Renal size in normal children. Archs Dis. Childh. 37 : 616 (1962).
9. HODSON, C.J. : Reflux nephropathy: scoring the damage; in Hodson, J., Kincaid-Smith. P., Reflux nephropathy. p. 29 (Masson, New York 1979).
10. KÄLLENIUS, G.; WINBERG, J. : Urinary tract infections treated with single dose of short acting sulphonamide. Brit Med. J. 1 : 1175 (1979).
11. KLARE, B.; AMMANN, P.; REINBOLD, F.; GEORGI, P.; MANZ, F., MÖHRING, K.; SCHÄRER, K. : Kidney size and split renal function in reflux nephropathy; in Hollenberg, N.K., Lange, S., Radionuclides in nephrology. p. 7 (Thieme, Stuttgart 1980).
12. KLARE, B.; GEISELHARDT, B.; WESCH, H.; SCHÄRER, K.; IMMICH, H.; WILLICH, E. : Radiological kidney size in childhood. Pediatr. Radiol. 9 : 153 (1980).
13. KUNIN, C.M. : Duration of treatment of urinary tract infections. Am. J. Med. 71 : 849 (1981).
14. NORMAND, I.C.S.; SMELLIE, J.M. : The child with urinary tract infection. Medicine 29 : 1588 (1977).
15. OLBING, H. : Harnwegsinfektionen bei Kindern und Jugendlichen. p. 55 (Thieme, Stuttgart 1979).
16. OLBING, H. : Nichtobstruktive Harnwegsinfectionen im Kindesalter: diagnostische und therapeutische Probleme. Diagnostik Intensivtherapie 6 : 364 (1981).
17. OLLING, S.; VERRIER-JONES, K.; MACKENZIE, R.; VERRIER-JONES, E.R.; HANSON, L.A.; ASSCHER A.W. : A four-year follow-up of schoolgirls with untreated covert bacteriuria: bacteriological aspects. Clin. Nephrol. 16 : 169 (1981).
18. Report of the International Reflux Study Committee: Medical versus surgical treatment of primary vesicoureteral reflux. Pediatrics 67 : 392 (1981).
19. SMELLIE, J.M.; KATZ, G.; GRUNEBERG, R.N. : Controlled trial of prophylactic treatment in childhood urinary-tract infection. Lancet ii : 175 (1978).

20. SMELLIE, J.M. : Antibiotische Prophylaxe rezidivierender Harnwegsinfektionen bei Kindern. Mschr. Kinderheilk. 129 : 328 (1981).
21. STEPHENS, F.D. : Cystoscopic appearances of the ureteric orifices associated with reflux nephropathy; in Hodson, J., Kincaid-Smith, P., Reflux nephropathy. p. 119 (Masson, New York 1979).
22. WINBERG, J.; ANDERSON, H.J.; BERGSTRÖM, T.; JACOBSON, B.; LARSON, H.; LINCOLN, K. : Epidemiology of symptomatic urinary tract infection in childhood. Acta Paediat. Suppl. 252 (1974).
23. WINBERG, J.; BERGSTRÖM, T.; JACOBSON, B. : Morbidity, age and sex distribution, recurrences and renal scarring in symptomatic urinary tract infection in childhood. Kidney. int. 8 : 101 (1975).