The Turkish Journal of Pediatrics 30:69-79, 1988

CLINICAL PYELONEPHRITIS OF INFANCY-AN OFTEN OVERLOOKED RENAL DISEASE*

*Jan Winberg MD***

The approximate incidence of significant renal diseases in industrialized countries is shown in Table I. In such countries, urinary tract infections (UTI) is not only the most common renal disease, but it is probably also the most common bacterial infection at least in females.

In countries with less well-developed health services, UTI is often said to be rare or non-existent. This may be incorrect since acute pyelonephritis (acute, febrile UTI) of infancy and early childhood is often overlooked. If so, this is serious since this disease –if untreated– may be responsible for part of acute early childhood death, for bladder and renal calculus disease, for hypertension and for chronic renal failure with onset later during childhood or adolescence.

The natural history of acute pyelonephritis in early childhood is shown in Table II. It is suggested that this study from Germany during the early years of this century may describe the natural course of febrile UTI today in countries where low access to medical aid still exists.

In the midst of the sixties about 40% of adults with terminal renal failure in Sweden had focal renal scarring (chronic pyelonephritis; reflux nephropathy). In most instances the renal damage was probably caused by early infantile pyelonephritis occurring in the pre-antibiotic era when there was no remedy available or during the forties or fifties when little attention was paid to care of patients with febrile UTI. In 1984 only 14% of adults with terminal renal failure had focal renal scars. These figures demonstrate that prevention of chronic renal failure due to infection is possible. Observation of individual cases clearly show the association: acute clinical pyelonephritis –renal scarring– damage of renal function –hypertension. Experience shows that an active search for UTI by systematic urine cultures and sediment examinations will increase the number of diagnosed cases of UTI severalfold. With this as a background, I will propose that statements about low incidence of UTI in developing countries be reexamined. This would probably be a priority in improving health service.

Below, the incidence, symptomatology, clinical and laboratory findings, diagnosis, prognosis, and treatment are discussed. Infections may involve the kidney

---

* From the Department of Paediatrics, Karolinska Hospital, Karolinska Institute, Stockholm, Sweden

** Professor of Pediatrics, Karolinska Institute.

Supported by the Medical Research Council, Grant 16X-0765.

(pyelonephritis) and/or the lower urinary tract (cystitis). This paper concentrates on infections involving the kidney. Cystitis and asymptomatic bacteriuria is not dealt with.

TABLE I: Incidence of Some Significant Renal Diseases in Childhood

Acute pyelonephritis 1st year of life - 1/100 children

Acute nephritic syndromes - low incidence
Chronic nephritic syndromes - low incidence

Idiopathic nephrotic syndrome 1-2/100,000 inhabitants

TABLE II: Prognosis in "Acute Pyelitis" in Infants and Small Children 1900-08 (104 cases)

Acute mortality	20%
Chronic illness*	20%
Spontaneous recovery	60%

* often "failure to thrive" picture.

Approximate figures of Göppert, 1908.

TABLE III: Definitions

UTI = urinary tract infections of any localization between urethra and kidney.

Acute pyelonephritis-bacterial infection of the kidney (usually febrile)

Cystitis or low infection - infection limited to the bladder

Focal renal scar = reflux nephropathy = chronic pyelonephritis

Definitions

The terminology is sometimes bewildering. Terms, as used in this paper, are listed in Table III. The typical infection-induced focal renal scar consists of damaged renal papilla and a wedge-shaped scar of the overlying parenchyma, as indicated in Fig. 1. Retardation of the growth of the kidney without demonstrable focal scar may be another consequence of an early renal infection.

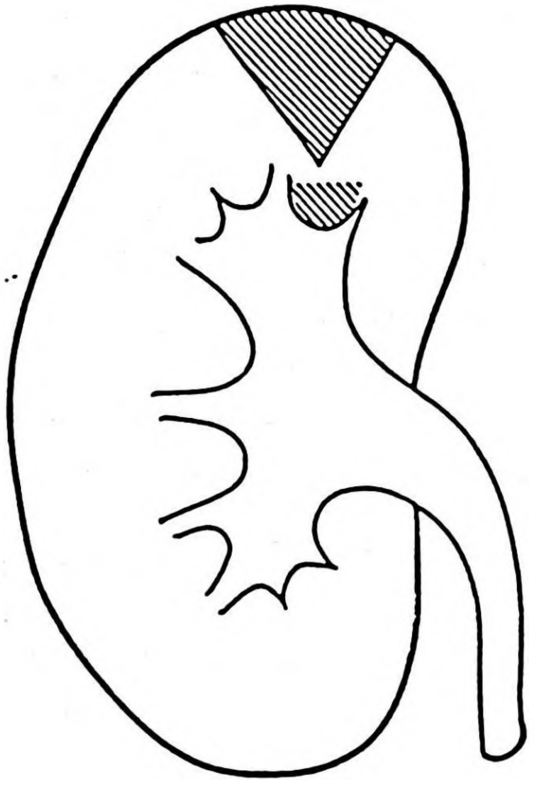

Fig. 1: Post infectious focal scar. Schematic drawing of the typical infection induced focal renal scar. It consists of a damaged papilla over which the renal parenchyma is destroyed segmentally, often with a very sharp border between damaged and undamaged kidney tissue.

Symptomatology and findings

The severe bacterial infection of the renal parenchyma may appear in two clinical forms: either as a febrile disease of acute onset and often without any other obvious symptoms or with a „failure to thrive" picture usually without fever.

During the first year of life and the subsequent 1-2 years, the characteristic symptom of the first infection is high fever. This corresponds to clinical pyelonephritis (i.e. involvement of the renal parenchyma), the incidence of which is highest in the first few years of life-the risk rate being 1-2% for males and females. UTI should be suspected in any small child with unexplained fever, especially if the child has been vomiting, is pale, irritable, sensitive to touch and if there is pain on palpation over the renal areas. *Smelly diapers may give a hint to*

the correct diagnosis. An abnormal micturition pattern may occur in small children, but its absence does not justify dismissal of the diagnosis. Overt abdominal pains and micturition disturbances become more common at about the age of four years. The external genitalia should be inspected for structural abnormalities and signs of vulvitis or balanitis. Malformations with obstruction of the urinary flow predispose to UTI. The lower abdomen may be raised and/or a tumor may be felt over the renal areas. Infections associated with obstruction may lead to a rapid destruction of the renal parenchyma. Early diagnosis of obstruction is therefore essential, so that normal urinary flow can be established. Similarly, the possibility of gross vesico-ureteric reflux (VUR) with dilation of the ureter and renal pelvis and intrarenal reflux must be examined. It is of great help if an intravenous pyelography or an ultrasound examination can be performed to exclude hydronephrosis or renal calculi and a micturition urethrocystography made to exclude a vesico-uretheral reflux with dilation (see below). In many places where these facilities are not available, clinical judgement should guide the further management.

Dealing with children with febrile UTI

The infantile kidney is highly vulnerable and one single attack of a febrile infection not taken care of adequately may result in one or more focal renal scars. There is much evidence to suggest that the first infection has a greater significance than subsequent ones, because the defence mechanisms of the very young child, without any earlier experience of pyelonephritogenic *Escherichia coli,* are inadequate to deal with pathogenic organisms before they reach the kidney. *Therefore, diagnosis and care of the very first infection may be the most important event in the care of childhood UTI and prevention of renal damage. Always, examine the urine for bacteria and cells in a child with fever of a nonobvious origin.*

A recent analysis of 75 children on a dialysis/transplantation programme in the UK showed that chronic pyelonephritis was the most common single disease in these patients. Reduction of this figure depends on the ability of general practitioners and general paediatricians to recognize patients with pyelonephritis among all small children presenting with fever.

Dealing with children with "failure to thrive".

"Failure to thrive" -slow weight gain, anorexia, vomiting, listlessness, anemia, etc. can be due to a great variety of conditions, among them a persisting urinary tract infection with or without hydronephrosis. An untreated acute febrile UTI may, after some time, turn into a "failure to thrive picture". In these instances the kidney may be at risk for permanent renal damage although the infection is nonfebrile. The diagnostic workup of an infant with "failure to thrive" should therefore always include a urine culture and a urine sediment examination.

Etiology

Acute febrile infections are almost exclusively caused by *E.coli.* Klebsiella may be common in neonates and Proteus among males after the first year of life. Gram-positive infections occur mostly among older children or adults.

Diagnosis and investigations

Demonstration of significant bacteriuria and pyuria are the cornerstones in diagnosis. The main obstacle in making a diagnosis in infants and toddlers is obtaining a urine specimen. Bladder puncture is expedient in infants, but often less acceptable in children over the age of one year. "Bagged" urine specimens are acceptable for sediment examination, but may be contaminated by bacteria from the external genitals. Positive cultures must therefore be evaluated cautiously, especially in boys in whom the prepuce normally contains large amounts of bacilli. After one year of age, the preputial flora becomes sparse.

Demonstration of white cells in the urine. Febrile UTI is almost always associated with pyuria. The degree of white cell excretion can be estimated either by direct counting of the number of white cells per cubic millimeter in unspun urine or after centrifugation of the urine. In febrile UTI the high power field is usually almost covered by white cells, sometimes being clumped together. In quantitative estimation in unspun urine more than 10-15 white cells in boys and more than 50-100 cells in girls is usually found in acute pyelonephritis.

Dipslide culture and Nitrite test

Dipslide cultures are cheap and accurate and avoid false-positive results caused by transport and laboratory delays. They can be used for testing patients with fever; in most instances they will give a tentative diagnosis within 12 hours. Correct reading is important, and usually easy in clear-cut cases of pyelonephritis. Contaminated samples with 2-3 species of bacteria as often seen in small boys may be misjudged as positive even if the count of each strain is low, say in the order of 10000-20000 bacteria/ml. Instruction in the reading of dipslides by a microbiologist or a competent technician can increase the competence of the staff and hence the accuracy of diagnosis.

The nitrite test can also be recommended. False-positive results are rare, but false-negatives are often seen in small children. A reasonable explanation would be that anorexia and vomiting is followed by low nitrate excretion in urine.

Examinations to exclude obstruction of the urinary flow or other anatomical abnormalities

This section is divided into two parts: what is desirable and what is practical. This may vary in different places.

What is desirable: radiographic examination

Girls less than three years of age should have an intravenous urography (IVU) and a micturition cystourethrography (MCU); girls over this age should have an IVU. This should be followed by a MCU only if there is recurrent infection or the IVU shows abnormalities such as dilation and scarring. All boys should preferably have an IVU and a MCU. The IVU should preferably be done within 2-3 weeks and the MCU within 2 months. To prevent iatrogenic infection during the MCU, nitrofurantoin, 3 mg/kg body weight, may be prescribed for one day.

Irrespective of age and sex, an early IVU is required in all unresolved cases (i.e., if the patient's temperature does not settle within a few days, or the urine sediment remains abnormal for more than 3-4 days).

An ultrasound examination is easy and accurate for diagnosis of obstruction with hydronephrosis. Where available this procedure is strongly favoured and can be done in the acute phase of the disease to exclude obstruction, and often replace an IVU.

What is practical: clinical and laboratory evaluation

The most important aim of radiological exploration is to diagnose obstructive malformations. calculi and gross reflux. When radiologic or ultrasound facilities are not easily available, one has to rely on clinical signs and simple laboratory findings in selecting those children who may need expert evaluation. Table IV lists findings where one may suspect that infection is complicated by obstruction or stones.

TABLE IV: Characteristics of Infections Complicated by Obstruction

Raised bladder after micturition
Mass in the loin
Dehydration
Hypertension
Acidosis
Raised blood urea
Bad response to treatment

A raised bladder after micturition in a boy indicates a low obstruction. Try to pass a catheter and leave it in place until expert advice can be obtained. A palpable mass in the loin may indicate a high obstruction. Hypertension may suggest severe renal parenchymal damage and so does a persistently high blood urea, not explained by dehydration. Acidosis is another important sign. If fever does not normalize after a few days and pyuria does not resolve, this may suggest the complications mentioned above or the presence of renal stones. In such

instances the child is in severe danger and every possible attempt to have an expert evaluation including radiology should be done.

Main determinants of renal damage

The aim of the care of patients with acute pyelonephritis is to prevent renal damage. The main risk factors of focal scarring and renal growth retardation are listed in Table V. The role of obstruction, calculi and gross reflux with intrarenal reflux in the occurrence of severe renal damage is mentioned above and is the reason for radiologic investigation. Other important factors are commented upon below.

TABLE V: Main Determinants of Renal Damage

Obstruction, stones
Gross reflux + intrarenal reflux
Low age
Therapeutic delay
Bacterial virulence
Host susceptibility

Age

The growing kidney of the young child seems to be much more vulnerable than that of an older child or adult. Particularly vulnerable are the kidneys of infants below the age of one year when also the frequency of acute pyelonephritis is much higher than later on. It is thus especially important to diagnose infections during the first year of life. This is at the same time difficult since in this age period the symptoms are often unspecific, i.e. fever and nothing more. Smelly urine or diapers may be of help in detecting infections.

Therapeutic delay

Another important determinant of renal damage is the duration of infection before treatment begins. A few days of persistent febrile infection may be sufficient to cause severe, irreversible renal and ureteral damage. This is shown by clinical observation and experimental studies.

Individual susceptibility

Some individuals are more prone to infections than others. This tendency is associated with an abnormal Gram-negative colonization of the periurethral area; uroepithelial cells from infection-prone females also bind *E.coli* more avidly than cells from non-susceptible ones. Such females may run a greater risk of renal damage.

Bacterial virulence

Bacteria may carry a great variety of virulence factors, but the ability to bind to epithelial cells by specific "adhesins" may be the most relevant. Such adhesion between bacteria and epithelial cells is mediated by *fimbriae* or *pili,* which are proteinaceous extensions from bacteria that recognize and bind to specific receptors on epithelial cells for those strains of *E.coli* that cause pyelonephritis. This structure is related to the antigens of the P blood group system. Corresponding fimbriae on the bacteria, responsible for the binding to the epithelial cell receptor, have consequently been named P-fimbriae. More than 90% of pyelonephritogenic *E.coli* are P-fimbriated. In cystitis and covert bacteriuria and in faeces from healthy controls, the frequency of P-fimbriated *E.coli* is much lower. P-fimbriae probably help the bacteria to resist the flow of urine by attaching to the uroepithelium, and may also help the bacteria enter the kidney. Receptors for P-fimbriae are present on uroepithelial cells and on tubular cells. Much work remains to be done until the ultimate role of P-fimbriae and of other adhesins is determined. The discovery of P-fimbriae and their specific carbohydrate receptor may open new possibilities for diagnosis, treatment and immunization.

Clinical importance of P-fimbriae

How do bacteria in the bladder reach the kidney? Gross vesico-ureteric reflux with intrarenal reflux may in many instances bring large numbers of bacteria into the renal parenchyma.

However, in many instances with renal infection, vesico-ureteric reflux is not demonstrable. Here P-fimbriae may explain the spread of the bacteria. Through the ability of P-fimbriated *E.coli* to cling to the epithelial surface of the ureters, and the turbulence of flow in the ureter, bacteria may be transported upstream to the kidney even in the absence of reflux. P-fimbriated *E.coli* also seems to cause a ureteral paralysis causing a functional obstruction of the ureter. This seems to be as effective as gross vesico-ureteric reflux with intrarenal reflux in causing pyelotubular backflow and infection of the renal parenchyma. Renal scarring may follow in either situation.

Prevention of renal damage

The prevention of kidney damage following UTI poses enormous problems. Prospective studies of the natural history of UTI have shown that kidney damage from febrile UTI occurs at a very early age. Experimental studies show that kidney scarring from infection can be prevented only if treatment is started very soon after the initiation of the infection. This, together with the fact that UTI in the young is difficult to diagnose because of the absence of localized symptoms and

the difficulty of obtaining urine for diagnostic purposes may explain why infective kidney scars remain so common. For example the prevalence of infection-induced kidney scars in apparently healthy school-girls has been shown to be up to 1 in 200 in industrialized countries. The lesson is that the urine must be looked at in *all* febrile children who lack localizing symptoms or signs and that treatment must be started *at once* if evidence of urinary infection is found. Appropriate care of infants with "failure to thrive" due to UTI is probably also of great importance.

TABLE VI: Programme of Follow-up during and after Treatment of Acute, Febrile Pyelonephritis and in Patients with a "Failure to Thrive Picture"

Time after onset of treatment	Acute pyelonephritis (temperature > 38 °C, CRP-positive)
3 days	Dipslide culture WBC in urine Possibly IVU* or US*
2-3 weeks	Dipslide WBC in urine CRP ESR Possible referral for radiological examination
2 months	Dipslide WBC in urine
3-4 months	Dipslide WBC in urine
12 months	Dipslide WBC in urine
Later	If possible, a check-up should be performed at 24 months and 36 months after onset

ESR = erythrocyte sedimentation rate
CRP = C-reactive protein
WBC = white blood cell count
IVU = intravenous urography
US = ultrasound examination

* If suspicion of obstruction is high.

Therapy, prophylaxis and follow-up of patients with acute febrile pyelonephritis

Infecting bacteria are usually sensitive to most commonly used drugs, but this may vary between different countries and different areas. Treatment of a patient with an acute febrile infection or a "failure to thrive" picture should last for 7-10 days. Amoxicillin and cotrimoxazole are good drugs, but almost any antibiotic will have an effect. Amoxicillin is given in a dose of 25-50 mg/kg body weight/24 hours. In countries where sulphonamide resistance is less common, *short acting* sulphonamides are recommended as the first choice since they are efficient, have few side effects and are inexpensive. Sulphafurazole and sulphasomidine can be given in doses of 100 mg/kg body weight/24 hours if the child is well hydrated. Small children, especially those under one year of age, should be given prophylaxis against re-infection until a micturition urethrocystography has been performed. In case this examination can not be done, prophylaxis should be continued for at least three months. Nitrofurantoin 1 mg/kg body weight/24 hours can be given. An ideal program for follow-up during and after treatment of pyelonephritis is suggested in Table VI. If such a thorough management is impossible the most important observation to be made is whether if after a few days of therapy have been completed, the bacteriuria and pyuria have been eliminated. If this is not the case, a complicating malformation should be suspected and an expert evaluation sought.

Summary

Clinical pyelonephritis is a common disorder of infancy and early childhood. The diagnosis seems to be frequently overlooked. It is recommended that all infants and children with febrile infection and all with a "failure to thrive" picture should have a urine examination (sediment, dipslide culture) if the cause of the disease is not obvious. Clinical pyelonephritis if untreated, may run with a high immediate mortality rate or often develop into a chronic disease (failure to thrive picture), as suggested by studies in the pre-antibiotic era. Renal calculi, hypertension and chronic renal failure are long-term consequences, the appearance of which may be delayed for one or more decades after an early infantile infection. With adequate care, the immediate and longterm prognosis is excellent, i.e. kidney damage due to infection is preventable.

Urinary tract infection is one of the most common bacterial infections in industrialized countries. There are very few reports of this disease from developing countries and its existence is sometimes questioned. Properly designed epidemiologic studies are urgently needed to see whether this disease is or is not a threat to child health in developing countries.

REFERENCES

1. Forfar JO, Arneil GC (eds). *Textbook of Paediatrics* (3rd ed). Edinburgh: Churchill Livingston, 1984.
2. Symposium on pediatric nephrology. *Pediatr Clin North Am* 29:775, 1982.
3. Winberg J. Urinary tract infection and reflux nephropathy in children. *Medicine International* 24:1101, 1982.