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Treatment of children with acute pyelonephritis: a prospective randomized study

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Abstract The aim of this study was to compare, in children with acute pyelonephritis, the efficacy of 7 days' (group A) and 3 days' (group B) intravenous antibiotics, both followed by an oral treatment. Children were randomized after 3 days of intravenous treatment. Technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy was performed within the first days after admission and repeated 6 months later. Total or partial persistence of renal abnormalities on the 6-month DMSA scintigraphy was used as the endpoint of the study. Among the 92 children included in the study, 87 were followed for at least 6 months (43 in group A and 44 in group B) and were eligible for analysis. Late DMSA was abnormal in 9 kidneys of group A and 12 kidneys of group B, representing respectively 24% and 44% of kidneys with abnormalities on the initial DMSA (difference statistically not significant). When the patients were stratified according to the delay of treatment, the percentage of patients with sequelae in group A was comparable, whether the delay was less or more than 1 week. In group B, the percentage of patients with sequelae was significantly higher ($P<0.01$) when the delay was more than 1 week.

Keywords Pyelonephritis · Urinary tract infection · Renal sequelae · Treatment · Randomization · Dimercaptosuccinic acid scintigraphy

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Introduction

Acute pyelonephritis (APN) is a common disease in children. However, the antibiotic treatment remains largely empirical. More specifically, whether antibiotics must be administered intravenously and for how long has been the subject of a limited number of studies. One of the problems in designing studies to evaluate the effectiveness of antibiotics in APN is to select an endpoint that might reflect the risk of long-term renal sequelae. Disappearance of clinical symptoms, sterile urines, or the absence of recurrence of urinary tract infection (UTI) are classically used as criteria to evaluate the efficacy of treatment, although they do not guarantee the absence of renal sequelae.

We report a prospective randomized study, in a population of children with high suspicion of APN, to compare the efficacy of two types of treatment: a 7-day intravenous antibiotic treatment, followed by 2 weeks of oral antibiotics, and a 3-day intravenous antibiotic treatment followed by 18 days of oral antibiotics. The presence of renal sequelae on technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy, 6 months after the acute episode, was used as endpoint.

Material and methods

Patients

Candidates for randomization

The prospective inclusion of new patients was started in December 1995 and ended in December 1998. All children aged 6 weeks to 15 years, admitted to hospital because of high suspicion of APN, were candidates for randomization. They were all severely ill: fever ≥38.3°C associated with variable combinations of clinical signs (septic aspect, loin pain, vomiting), biological alterations (sedimentation rate >30 mm/h, increased C-reactive protein, leukocyte count >15,000 with more than 50% neutrophils), and urinalysis revealing abnormal amounts of leukocytes(>5 WBC/mm^3) and/or bacteria. An additional condition was the absence of other focal infection. Patients with first as well as with recurrent UTI, with or without known vesicoureteric reflux, were eligible.

Only those with proven UTI were included in the study. In children younger than 3 years of age, a urine sample was obtained by means of suprapubic puncture whenever possible, and UTI was considered as present with growth of urinary pathogens in any number in that single sample. When a suprapubic puncture was not performed, urine samples were obtained using perineal bags and a single microorganism had to be found, with more than 100,000 cfu/ml, ideally in three cultures and at least in two. Midstream urines were used in older children.

Patients with negative or equivocal urine cultures were not included in this study. The results of imaging procedures (renal ultrasonography and DMSA scintigraphy) were not taken into account for the purpose of inclusion or exclusion.

In all these children, intravenous treatment with temocillin, a beta-lactam antibiotic with a wide-spectrum activity against gram-negative bacteria but no activity against gram-positive organisms, was initiated at a dose of 25 mg/kg body weight within the first hours after admission. This treatment was adapted if the urine culture revealed gram-positive organisms.

Randomization

After 3 days of intravenous treatment (6–7 doses temocillin), the possible criteria for rejection (negative culture, etc.) were evaluated by the physician responsible of this study. The patients were then randomized: either the intravenous treatment was continued for another period of 4 days (group A) or was replaced by an oral treatment (group B) chosen according to the antibiogram. Amoxycillin (50 mg/kg body weight in 3 doses, maximum 2 g/day) was the first choice; amoxycillin plus clavulanic acid (50 mg/kg per day in 3 doses, maximum 2 g/day) was chosen in case of amoxycillin resistance.

All patients (group A and B) remained hospitalized for 7 days in total, in order to avoid any bias related to compliance. At the end of day 7, oral treatment was started in group A and continued until day 21 for both groups. At day 21, chemoprophylaxis was started, generally nitrofurantoin at a dose of 2 mg/kg in one daily dose. Since the patients with vesicoureteric reflux received this prophylaxis for prolonged periods, it was decided that all patients included in the study would receive this prophylaxis for the 6-month duration of the study, in order to avoid possible bias.

Informed consent

Parents were fully informed about the study protocol, and that there was no a priori advantage of either regimen. They had to give informed consent. Consent of the patient's family practitioner or pediatrician was also requested before the decision of randomization. The study was approved by the ethics committee of the institution.

Exclusion criteria

Exclusion criteria included severe renal problems, such as urethral valves in male infants, hydropyonephrosis, and abscess, fever (>38°C) within 24 h of randomization, bacteria resistant to any usual oral treatment, effective oral treatment given before admission, technical problems related to intravenous administration, parents or house doctor refused the randomization.

Additional investigations

Blood sampling and urine cultures

Leukocytes counts, sedimentation rate, C-reactive protein, urea, and creatinine were measured on admission, after 48 h, and after 7 days of treatment. Control urine cultures were performed at 7 days, 6 weeks, 3 months, and 6 months, and more if clinically indicated.

Renal ultrasonography

Renal ultrasonography was performed within the first 3 days of admission by a pediatric radiologist. In the present study, it was principally used for the diagnosis or exclusion of underlying structural pathology, such as small kidneys, severe obstructive pathology, and expansive lesions. Attention was also paid to manifestations of APN, such as swelling of the kidney, increased thickness of the pelvic wall, and focal lesions. They were, however, not taken into account in this study.

DMSA scintigraphy

Tc-99m DMSA scintigraphy was performed within 3 days of admission and repeated 6–7 months later. Images were obtained by means of a gamma camera equipped with a high-resolution collimator 2–4 h after an intravenous injection of Tc-99m DMSA, according to the recommendations of the European Pediatric Nuclear Medicine Task Group [1]. One posterior and 2 posterior oblique views were obtained, often with zoom magnification and/or pinhole collimator.

For each kidney, the possible responses were: normal, abnormal, or equivocal. The criteria for normality have been recently evaluated [2]. An equivocal answer was given when it was difficult to decide about normality or abnormality. Because of the difficulty in dealing with the equivocal results, it was decided to analyze the data in two ways, either by excluding them, or by including them in some way. For the last option, the equivocal readings only on the initial scintigraphy were considered to be normal. Equivocal readings on late scintigraphy were considered to be normal if the initial scintigraphy was normal. Late equivocal readings were considered to be abnormal if the initial scintigraphy was abnormal. The same observer who reported the early scan also reported the late scan, without knowledge of the results of the early scan. Moreover, the report on both the acute and late scintigraphy was made without knowledge of the type of treatment received by the patient.

Finally, a comparison was carried out between early and late scintigraphy, and the scintigraphic evolution was classified for each kidney in one of following categories, in increasing order of severity: kidney normal and unchanged; lesions disappeared; considerable improvement; slight improvement; lesions unchanged; new lesion.

Micturating cystourethrography

Micturating cystourethrography was performed in all patients 6 weeks after APN.

Follow-up

Patients were seen at 3 weeks, 6 weeks, 3 months, and 6 months in the outpatient clinic after discharge from hospital. Recurrence of infection and compliance with treatment and prophylaxis were checked.

Endpoints

Persistence or recurrence of UTI

Persistence of positive urine culture on day 7 after admission was considered as negative endpoint for evaluation of the effect of treatment. Recurrence was considered as a failure of the chosen treatment if the recurrence occurred within the first 6 weeks after randomization.

Renal sequelae

Development of renal sequelae was used as "surrogate endpoint" in place of long-term clinical complications. Sequelae were defined as the partial or complete persistence of renal abnormalities on the 6-month DMSA scintigraphy, compared with the early DMSA scan.

Drop-outs

Some patients were lost to follow-up. Because of the absence of a late DMSA scintigraphy, they were not included in the analysis of renal sequelae.

Statistical analysis

Two-by-two contingency tables were analyzed using chi-squared test or, in the case of small numbers, Fischer's exact test.

Results

Diagnosis of UTI

In 43% of the 51 children below 3 years of age, the diagnosis was based on urine obtained from suprapubic puncture. In the remaining patients below 3 years of age as well as in the older patients, 3 positive cultures (more than 100,000 cfu/ml of one single microorganism) were available in 2 of 3 patients, and 2 positive cultures in 1 of 3 patients. Ninety percent of the patients had more than 10 leukocytes/mm^3 on urinalysis and an additional 5% had 5–10 leukocytes/mm^3. The three cultures were obtained in all cases within the first 12 h of admission, and in most cases within the first 6 h.

Randomization

Among the 103 children with a high suspicion of APN initially treated intravenously, 92 were included in the study and randomized, and 11 were not, according to the exclusion criteria.

Drop-outs

Two patients were excluded from the analysis during the hospital stay, 1 because of intolerance to any oral treatment and 1 because of an error in randomization. Later, 3 patients among the remaining 90 did not undergo the 6-month follow-up. Therefore, 87 patients remained eligible for analysis, 43 in group A and 44 in group B.

Characteristics of patients at entrance

The characteristics of the patients are described in Table 1. Group A patients were slightly older and had more DMSA abnormalities, expressed both in number of patients and in number of kidneys. The differences between the two groups were, however, not significant. At the time of randomization, all children were afebrile according to the exclusion criteria. Moreover, all were clinically asymptomatic. Plasma creatinine was in the normal range in all patients.

Recurrence of UTI

During hospitalization, all urine cultures were negative on day 7. During follow-up, 5 children had symptomatic

Table 1 Characteristics of patients (*UTI* urinary tract infection, *DMSA* dimercaptosuccinic acid, *E. coli Escherichia coli*)[a]

	Group A*	Group B
No. of patients	43	44
Median age (months)	25	20
Minimal age (months)	2	3
Maximal age (months)	182	179
Less than 12 months	13(30)	17(39)
Less than 24 months	20(47)	25(57)
Past UTI	8(19)	8(18)
Known urological malformations	4(9)	1(2)
Urological surgery	1(2)	1(2)
Chills, septic aspect	9(21)	9(20)
Vomiting	12(28)	11(25)
Fever >38.5°C	43(100)	42(95)
Fever 38.5°C–39°C	16(37)	19(43)
Fever 39.1°C–40°C	21(49)	16(36)
Fever >40°C	6(14)	9(20)
Costovertebral tenderness	16(37)	11(25)
Positive blood culture	2(5)	0(0)
Leukocyturia (>5 WBC/mm^3)	41(95)	42(95)
Microscopic hematuria	25(58)	23(52)
Bacteriuria	40(93)	35(80)
Urine culture positive for *E. coli*	43(100)	43(98)
Resistance to amoxycillin	21(49)	19(43)
Patients with abnormal early DMSA scan	33(77)	26(59)
Kidneys with abnormal early DMSA scan	37(43)	28(32)
Bilateral involvement on early DMSA scan	3(7)	2(5)

* No significant difference between group A and group B, for all parameters considered

[a] Percentages are given in parentheses

recurrence of UTI, all with *Escherichia coli* resistant to amoxycillin; 2 developed UTI 3 weeks after discharge (1 in group A and 1 in group B); the 3 other UTI episodes occurred between 3 and 6 months (2 in group A and 1 in group B). All were treated for 15 days with amoxycillin and clavulanic acid.

Equivocal results

Five kidneys (2 in group A and 3 in group B) were reported as "equivocal" on the early scan and normal on late scan. Five kidneys were reported as "equivocal" on the late scan. In 3 the early scan was abnormal (1 in group A and 2 in group B). In 2 the early scan was normal (1 in group A and 1 in group B).

Renal sequelae

Of the 87 children included in the study, 19 (22%) presented abnormalities on late scintigraphy. When only those children with abnormal initial DMSA scans were considered (59 children), 32% remained with sequelae. The same percentage (32%) was found if the number of kidneys with renal sequelae was expressed as a percentage of the initially abnormal kidneys. Very similar results were found when the 10 "equivocal" kidneys were not taken into account (29% of patients with initially abnormal kidneys and 29% of initially abnormal kidneys).

The following factors had no effect on the development of renal sequelae: age, gender, intensity of fever, intensity of inflammatory biology, and repeated infections before entering the study. Vesicoureteric reflux was observed in 35% of patients (38% in group A and 33% in group B) and renal sequelae were observed in 53% and 22% of patients respectively with and without vesicoureteric reflux ($P<0.05$).

Late DMSA findings in group A and B

Expressed in number of patients

In group A, 8 patients had an abnormal late DMSA scan (Table 2). This represented 19% of the 43 patients of this group and 24% of those 33 patients with abnormal initial DMSA sans. In group B, 11 patients had an abnormal late DMSA scan, accounting for 25% of the 44 patients of this group and 42% of the 26 patients with abnormal initial DMSA scans. When the equivocal cases were excluded, late sequelae were found in group A and B, respectively in 21% and 38% of the patients with initially abnormal DMSA scans.

Expressed in number of kidneys

In group A, 9 kidneys were abnormal on late DMSA scan (Table 3). This represented 10% of the 86 kidneys of this group and 24% of the 37 initially abnormal kidneys. In group B, 12 kidneys were abnormal on late DMSA scan, accounting for 14% of the 88 kidneys of this group and 43% of the 28 initially abnormal kidneys. When the equivocal cases were excluded, kidneys with late sequelae were found in group A and B, respectively in 22% and 38% of patients with initially abnormal DMSA scans.

Table 2 Late DMSA scintigraphy findings in group A and B (patients)*

Early DMSA \ Late DMSA	Normal	Abnormal	Total
Group A			
Normal	10	0	10
Abnormal	25	8	33
Subtotal	35	8	43
Group B			
Normal	18	0	18
Abnormal	15	11	26
Subtotal	33	11	44
Total	68	19	87

* The number of patients with late DMSA abnormalities (expressed as a percentage of all patients, as well as a percentage of the initially abnormal scans) was not significantly different in group A and in group B

Table 3 Late DMSA findings in group A and B (kidneys)*

Early DMSA \ Late DMSA	Normal	Abnormal	Total
Group A			
Normal	49	0	49
Abnormal	28	9	37
Subtotal	77	9	86
Group B			
Normal	60	0	60
Abnormal	16	12	28
Subtotal	76	12	88
Total	153	21	174

* The number of kidneys with late DMSA abnormalities (expressed as a percentage of all kidneys, as well as a percentage of the initially abnormal kidneys) was not significantly different in group A and in group B

Statistical comparison

The differences observed between group A and group B, whether they were expressed in number of patients or in number of kidneys, were not significant.

Comparison of residual and initial DMSA scan abnormalities

The importance of the residual lesions was variable. In 14 kidneys (6 in group A and 8 in group B), the compari-

son between early and late DMSA scan (Table 4) revealed that the lesions were unchanged or showed only slight improvement, corresponding therefore to an unfavorable evolution. In 7 kidneys (3 in group A and 4 in group B), only small residual lesions remained and the improvement was considerable. Three of them (1 in group A and 2 in group B) were equivocal lesions on late DMSA scan. Again, whatever the evolution of the residual lesions, the differences between group A and B were not significant, whether the equivocal results were or were not included.

Relationship between recurrent infections and sequelae on late DMSA scan

The proportion of sequelae among patients with a history of past UTI was similar in group A (3/7) and group B (3/8). Among the patients who developed UTI during the 6 months of follow-up, sequelae were observed in 2 of 3 patients in group A and in 1 of 2 patients in group B.

Duration of symptoms at the time of hospital admission and relationship with renal sequelae

Hospital admission occurred within the first 3 days of the beginning of symptoms in 67% and 68% respectively for group A and B. The treatment was delayed for more than 7 days in 21% in group A and in 14% in group B.

When delay between first clinical symptoms and admission was equal to or more than 7 days, 60% of these patients presented sequelae, while only 24% had persistent abnormalities when the delay was less than 7 days ($P<0.05$).

Table 4 Residual lesions compared with the initial lesions*

Evolution of the lesion	Number of lesions	
	Group A	Group B
Unchanged	3	3
Slight improvement	3	5
Considerable improvement	3	4
Total	9	12

* No significant differences between group A and group B

In group A, the statistical analysis was not able to show a significant difference in the percentage of kidneys with sequelae (evaluated on the number of initially abnormal kidneys), whether the delay was less or more than 1 week (Table 5).

In group B, the percentage of patients with sequelae was significantly higher when the delay of treatment was more than 1 week, than when the patients were treated more rapidly (Fischer exact test $P<0.01$). When comparing directly group A and group B for those patients with a delay in treatment of more than 7 days, the percentage of sequelae was not significantly different in both groups, although a trend was found for more sequelae in group B (Fischer exact test $P=0.07$). The effect of delay of treatment was independent of the presence or not of vesicoureteric reflux, since 50% of patients with renal sequelae and long delay of treatment had no reflux. The equivocal late DMSA results were all observed in patients without delay of treatment, and the results were not different when these equivocal results were not included in the analysis.

Discussion

UTI is common in children. About 1% of boys and 3% of girls experience at least one episode of UTI before the age of 11 years [3]. There is currently no consensus on the ideal route of antibiotic administration (oral or intravenous), and on the duration of this treatment [3, 4, 5, 6, 7, 8]. As reported by Jodal [9], the choice of antibiotic regimen is largely empirical and based on local practice. The only recent prospective randomized study, performed by Hoberman et al. [10], compared 14 days of treatment with a third-generation oral cephalosporin with an initial intravenous treatment with cefotaxime for 3 days, followed by oral cefixime for 11 days. The use of 14 days of oral cefixime was found to be a safe and effective treatment.

During these last few years, the practice in our department has been to administer systematically a 7-day intravenous treatment to all patients with APN. We have elected to compare a 3-day with a 7-day intravenous treatment, since a potential 4-day reduction of intravenous treatment and early discharge from the hospital represents a significant benefit for a young patient and his family. The choice of temocillin as initial intravenous

Table 5 Patients with initially abnormal kidneys. Number of kidneys with late renal sequelae in relation to the delay before treatment*

Delay \ Late DMSA	Group A		Group B	
	Normal	Abnormal	Normal	Abnormal
<7 days	24	6	16	7
≥7 days	4	3	0	5

* Comparison of the number of kidneys with sequelae in patients with and without a delay ≥7 days: group A NS, group B $P<0.01$
Comparison of the number of kidneys with sequelae in group A and B: delay <7 days NS, delay ≥7 days $P=0.07$ (NS)

treatment was based on the high prevalence of *E. coli* and the spectrum of activity of this antibiotic being limited to gram-negative organisms. The clinical staff was, however, prepared to change this treatment in case of identification of gram-positive bacteria in the urine.

In most of the cases, the randomization was well accepted by the families after an explanation of the various existing therapeutic attitudes and the absence of a consensus in this field. Similarly, the parents were generally aware of the importance of close follow-up during the next 6 months and the number of drop-outs was rather low.

We have used microbiological and radioisotopic endpoints to evaluate the effectiveness of treatment. In the present study, all patients had negative urine cultures after the 1st week of treatment. However, microbiological criteria are not very convincing (urine samples are generally sterile after a few hours of treatment [3, 11]), but this does not guarantee the absence of renal sequelae [12]. Inhibition of bacterial growth in vitro does not mean that the renal parenchyma is sterile. During follow-up, the number of episodes of recurrence of UTI, in particular within the first 6 weeks, was low and similar in group A and group B. Recurrence of infection some months after the initial treatment is probably not related to the efficacy of this initial treatment.

Since it is difficult to await the long-term clinical consequences of APN to evaluate the effect of treatment on late sequelae, the development of renal scarring may be used as a "surrogate endpoint." DMSA scintigraphy is presently considered as a valid technique for estimating the presence and the extension of acute lesions as well as the development of permanent sequelae. The technique is sensitive [12, 13, 14, 15], the inter-observer reproducibility is good [16], and experimental studies have validated the technique for both acute and chronic lesions [17, 18, 19, 20, 21, 22]. A consensus has been reached concerning most of the technical aspects related to the technique [2].

In the present study, both early and the late DMSA scans were performed, since it was important to evaluate whether a normal kidney on late DMSA scan was also normal during the acute phase or was the consequence of a perfect healing process. The late DMSA scan was performed 6 months after the early scan because it has been shown [23] that the abnormalities seen at 6 months will rarely improve later. The equivocal reports constituted a problem. It was decided to consider the early equivocal DMSA results as normal, since all the late controls of these equivocal scans were normal. However, the late equivocal scans were all considered as abnormal when the early scan was abnormal in the same area, bearing in mind that these equivocal findings could represent minimal residual lesions. However, the number of equivocal reports on late DMSA scan was small and the overall results were not different whether these equivocal results were included in the analysis or not.

The age of the patient has been a matter of discussion. In their recent prospective randomized study, Hoberman et al. [10] enrolled only children below 2 years of age, because some authors have identified infants aged <1 year as a group at particularly high risk for renal scarring [24]. In the present study, children of all ages (except those below 6 weeks) were included, based on the fact that other authors observed a high frequency of renal abnormalities in older children presenting with a first UTI [25, 26].

This study revealed a high number of acute lesions on DMSA scan, and it is obvious that the population selected on the clinical and biological criteria had a high probability of APN. Compared with the high number of acute lesions, the number of kidneys with late sequelae was less than 15% of the total number of kidneys, whatever the treatment. Whether some of these residual abnormalities were the consequence of the actual episode of infection or were pre-existing (previous infections or congenital defects) cannot be determined. This is a methodological limitation of the study.

When expressed in number of initially abnormal kidneys, the total number of sequelae was higher in group B than in group A. This difference was not statistically significant because of the rather small number of patients. This could not be explained by the initial characteristics of the patients, such as age, gender, or number of past infections. The difference became statistically significant when the patients were stratified according to the delay between first symptoms and admission. For patients of group B, when the delay was more than 7 days, the proportion of residual lesions was significantly higher than when the delay was shorter.

In the recent prospective randomized study of Hoberman et al. [10], on a larger population of patients, the design was somewhat different. Using the same endpoint based on early and late DMSA scintigraphy, the authors compared 14 days of oral treatment with 3 days of intravenous treatment followed by 11 days of oral treatment. They found no significant differences between these groups. It is however not impossible that a more-prolonged intravenous treatment, as in our present study, might be more effective, particularly in those patients where the diagnosis has been late. In another recent study [27], a 10-day intravenous treatment did not decrease the incidence of renal scars compared with a 3-day intravenous therapy.

It is obvious, however, that other factors, such as compliance of the patient with oral treatment, might influence the decision for intravenous treatment or at least for prolonged oral treatment during hospital admission.

In conclusion, the number of kidneys with sequelae was higher in the group having received a short course of intravenous antibiotics, but this difference was statistically not significant. Longer intravenous therapy might be beneficial in those patients with DMSA abnormalities during the acute phase of infection. In cases of delay of treatment, there might be some evidence that the long course of intravenous antibiotics is more effective.

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