Randomized Trial of Oral Versus Sequential IV/Oral Antibiotic for Acute Pyelonephritis in Children
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**OBJECTIVE:** To confirm whether oral antibiotic treatment is as efficacious as sequential intravenous/oral antibiotic treatment in the prevention of renal scarring in children with acute pyelonephritis and scintigraphy-documented acute lesions.

**METHODS:** In a prospective multicenter trial, children aged 1 to 36 months with their first case of acute pyelonephritis, a serum procalcitonin concentration $\geq 0.5$ ng/mL, no known uropathy, and a normal ultrasound exam were randomized into 2 treatment groups. They received either oral cefixime for 10 days or intravenous ceftriaxone for 4 days followed by oral cefixime for 6 days. Patients with acute renal lesions detected on early dimercaptosuccinic acid scintigraphy underwent a follow-up scintigraphy 6 to 8 months later.

**RESULTS:** The study included 171 infants and children. There were no significant differences between the 2 groups in any clinical characteristic. Initial scintigraphy results were abnormal for 119 children. Ninety-six children were measured for renal scarring at the follow-up scintigraphy (per protocol analysis population). The incidence of renal scarring was 30.8% in the oral treatment group and 27.3% for children who received the sequential treatment.

**CONCLUSIONS:** Although this trial does not statistically demonstrate the noninferiority of oral treatment compared with the sequential treatment, our study confirmed the results of previously published reports and therefore supports the use of an oral antibiotic treatment of primary episodes of acute pyelonephritis in infants and young children.
Urinary tract infections (UTIs) are common in childhood. UTIs affect up to 3.5% of children in the United States annually.⁴ Febrile UTI is a serious bacterial infection because of its potential to produce renal scarring. Not all febrile UTIs are acute pyelonephritis (APN); only up to two-thirds of children with a UTI accompanied by fever have acute parenchymal infection, with acute lesions on dimercaptosuccinic acid (DMSA) scintigraphy,²–⁶ which is the definitive diagnosis of APN.⁶–⁸ A serum procalcitonin (PCT) concentration >0.5 ng/mL predicts renal involvement.⁶,⁹–¹¹

The standard initial treatment of infants and children with APN has been intravenous antibiotic treatment. In a recent Cochrane review, Hodson et al reported that there were no significant differences in the risk of renal scarring between long intravenous treatment (8–15 days) and a sequential treatment consisting of intravenous antibiotics (2–4 days) followed by oral treatment.⁸ Three prospective trials have suggested that children with APN could receive an entirely oral antibiotic treatment without increased risk of renal scarring 6 to 12 months later.²–⁴ However, children receive different treatments in different parts of the world and also in different regions of the same country.¹²,¹³

Our hypothesis was that oral antibiotic treatment is as equally efficacious as sequential treatment with respect to the presence of renal scarring 6 to 12 months later in 1- to 36-month-old children with APN and scintigraphy-documented acute lesions.

METHODS

Ten pediatric units collaborated in a prospective randomized trial to compare the effects of oral and sequential antibiotic regimens in children having their first episode of APN. Patients were recruited from August 2004 to April 2008. The study was conducted with approval obtained from the Ethics Committee of the Direction de la Recherche Clinique. Written informed consent was obtained from both parents.

Inclusion Criteria

Infants and children, aged 1 to 36 months, were recruited from patients who presented at an emergency department (ED) with a first febrile UTI. Febrile UTI was defined as fever (≥38.5°C) with no alternative source for the fever and positive urinalysis (white cell counts ≥10⁵/mL) and Gram-negative rods in Gram-stained urine. Urine specimens were collected by catheter in infants or by midstream catch in older children. If sterile urine bags were used, 2 concordant consecutive urinary cultures were required. When urinalysis was positive for leukocytes and a Gram-negative strain, a blood sample was analyzed for PCT, either directly using a quantitative assay or by using a semiquantitative measurement (results given as ≥ or <0.5 ng/mL), depending on the ED. Only patients with PCT concentrations ≥0.5 ng/mL were included. In cases of semiquantitative PCT measurements, a quantitative measurement was done on the next working day. Patients had normal findings on prenatal ultrasonography, no known uropathy, and no uropathy suspected after ultrasound examination at inclusion.

For better visualization of inflammatory lesions in the acute phase, scintigraphy should be performed as soon as possible after the onset of symptoms, ideally within 2 days and not exceeding 10 days.³ We decided to perform DMSA scintigraphy within the first 8 days after inclusion. Only patients with acute lesions detected on early DMSA scintigraphy underwent follow-up and scintigraphy 6 to 8 months later.

We excluded infants and children with the following characteristics:

- Aged <1 month, prematurely born with a corrected age of <1 month, or aged ≥6 months
- Initial ultrasound exam revealing obstructive uropathy, renal hypoplasia, or signs of renal abscess
- Allergy to the study drugs
- Received antibiotic treatment in the 5 days before inclusion
- Patients judged as severely ill (prolonged capillary refill; high or low blood pressure)
- Vomiting or diarrhea that could have precluded administration of oral antibiotics
- Refusal from 1 or both parents
- Parental misunderstanding or uncertain adherence
- No Medicaid

We secondarily excluded infants and children with the following:

- Urinary culture with no bacteria, more than 1 type of bacteria, or bacteria resistant to the study antibiotics
- Serum PCT concentration <0.5 ng/mL after quantitative measurement
- Normal initial DMSA scintigraphy
- Recurrence of pyelonephritis before the second DMSA scintigraphy

Randomization

All study patients were included following the diagnosis of probable pyelonephritis at their first consultation in the ED, before the results of urine culture and DMSA scintigraphy. Immediately after recruitment, a computer-generated code was used (clean web) to assign the patients to receive either the oral treatment or the sequential treatment. Randomization was blocked and stratified according to centers and age at inclusion (≤1 year/1 year). In the oral group, patients received cefixime for 10 days, which consisted of an initial double-dose (8 mg/kg).
administered in the ED followed by 4 mg/kg twice daily. In the sequential group, patients received 50 mg/kg ceftriaxone intravenously once daily for 4 days followed by 4 mg/kg cefixime orally twice daily for 6 days. Antibiotic therapy was started after the urine and blood samples had been analyzed and the ultrasound exam had been performed. In both groups, cefixime bottles were given to the parents before discharge from the hospital.

Depending on local protocols, children were admitted for the first 12 hours then were treated as outpatients or stayed in the hospital at the discretion of the treating physician.

Follow-up
During the first days of treatment, temperature was taken every 6 hours until apyrexia (<38°C) persisted for >24 hours. The number of stools per day was also noted. All patients had a follow-up visit on day 4. Temperature and number of stools data were collected at this time. Patients with persistent fever at day 4 had a second PCT analysis and urinalysis performed.

After the initial 10-day treatment was completed, children remained on antibiotic prophylaxis (cotrimoxazole if possible, or another antibiotic adapted to prevent bacterial resistance) until voiding cystography (VCG) could be carried out (within 1 month). Antibiotic prophylaxis was discontinued if the VCG was normal. The patients then had a follow-up by their local physician, who informed the study centers in cases of recurrent pyelonephritis.

Renal DMSA Scintigraphy
Patients underwent a first DMSA scintigraphy within 8 days of inclusion. 99m Tc-DMSA renal scans were performed 3 to 4 hours after injection of a weight-scaled dose of DMSA. Acute scintigraphic pyelonephritis was defined as focal or diffuse areas of decreased DMSA uptake without evidence of cortical loss. All the renal scans were reviewed secondarily by 2 independent nuclear medicine experts, who were unaware of the treatment that had been assigned to the patients. For only those patients with abnormal acute phase scintigraphy, we scheduled another scintigraphy 6 to 8 months later to detect any renal scarring at the site of the original pyelonephritis.

Statistical Methods
We carried out exploratory analysis of risk of renal scarring depending on age, gender, PCT value, and vesicoureteral reflux (VUR) in both treatment groups. To test the noninferiority with respect to renal scarring of the oral antibiotic therapy versus sequential therapy, the trial sample size was determined by assuming an incidence rate of renal scarring of 20% in the 2 groups and an equivalence margin of 10%. α and β risks were fixed respectively to 5% and 10%. By using a 2-sided test approach, sample size was determined to be 349 subjects per group.

The categorical data of the study groups were compared by using the χ² test or the Fisher exact test, where appropriate. Quantitative data were compared by using the Wilcoxon rank test. The noninferiority hypothesis of the oral treatment compared with the sequential treatment was assessed by computing the 95% confidence interval (CI) of the renal scarring incidence difference and determining whether it contained the noninferiority margin (do not reject the inferiority hypothesis) or not (reject the inferiority hypothesis and accept the noninferiority hypothesis at the 95% level). All computations were performed by using SAS software V9.2 (SAS Institute, Cary, NC).

RESULTS
The pediatric EDs participating in the trial recruited 171 children who were having their first case of APN. Children were randomized into either the oral treatment group (cefixime, n = 85) or the sequential treatment group (n = 86). The demographic and clinical characteristics of the 171 children are shown in Table 1. No significant differences were found between the 2 groups. The mean serum PCT concentration for the oral group was not different from that of the sequential treatment group. All patients had an ultrasound exam before randomization, and no patients had signs of obstructive uropathy, renal hypoplasia, or renal abscess.

Escherichia coli were isolated from the urine of 100% of the children (Table 1). Therefore, only 1 of the 161 E coli isolates was resistant to all β-lactamins. Fifty-two children who had been accepted into the study were subsequently eliminated during the first week (Fig 1). One hundred and nineteen children, who had been correctly
allocated to a treatment group, had an abnormal initial scintigraphy and were subjected to an intention to treat (ITT) analysis. They were scheduled for a follow-up scintigraphy 6 to 8 months later. Of these, 23 patients did not complete the study (Fig 1). In the ITT analysis, children who had an abnormal first scintigraphy but did not undergo the follow-up scintigraphy were considered to have renal scarring. Ninety-six children completed the trial and were measured for renal scarring (per protocol analysis, PPA).

Primary Outcome: Renal Scarring

The 2 groups were not significantly different from each other, either in the ITT or in the PPA (Table 2). In the ITT analysis, the incidence of renal scarring was 41% (95% CI: 28.7%–53.3%) for children in the oral treatment group and 44.8% (95% CI: 32%–57.6%) in the sequential treatment group (risk difference: –3.8%; 95% CI: –21.6% to 13.9%). In the PPA, the frequency of renal scarring was 30.8% (95% CI: 18.3%–43.3%) in the oral treatment group and 27.3% (95% CI: 14.1%–40.5%) for the sequential treatment group (risk difference: +3.5%; 95% CI: –14.7% to 21.7%).

In the PPA, the incidence of scarring in the both treatment groups did not differ between children aged <1 year and children aged 1 to 3 years. The incidence of scarring also did not differ with respect to gender (Table 3). In the subgroup of 10 children <3 months, there were no infants with renal scarring in oral group (n = 4) and 2 infants with renal scarring (n = 6) in the sequential group.

Follow-up

Duration of Fever

Time to apyrexia did not differ between the 2 treatment groups (median: 24 hours; Table 1). Only 2 patients had fever on day 4. Both children were excluded from the study because of violation of antibiotic protocol. The first urinalysis of 1 child revealed an E coli strain resistant to all β-lactams, and he received another antibiotic treatment. The second child also had gastroenteritis and received a ceftriaxone treatment longer than that of the standard study protocol.
No child received any other treatment, and the 2 groups did not differ in the rate of hospitalization.

**Side Effects**

Two children did not tolerate cefixime because of vomiting, and treatment was changed to parenteral therapy. One child with apparent sepsis received intravenous ceftriaxone instead of oral cefixime.

One child in the oral treatment group had recurrent APN 3 days after the end of the treatment. His PCT concentration was 7 ng/mL, and apyrexia occurred 24 hours after beginning the oral treatment. In his urinalysis, the *E coli* strain was not resistant to cefixime.

**Serum Procalcitonin**

The mean serum PCT concentration was higher in children with renal scarring (n=28; median: 3.2 ng/mL; quartiles: 1.8–12.1 ng/mL) than in children without scarring (n=66; median: 1.7 ng/mL; quartiles: 1–4.1 ng/mL; P = .002).

**VUR**

Voiding cystography was performed for 152 children, of which 40 were found to have VUR (26.3%). We found 7 grade I, 18 grade II, 10 grade III, and 5 grade IV cases of VUR. In the subgroup per protocol, we detected VUR in 22 of 95 children (one child did not have a VCG). Regardless of VUR grade, renal scarring was similar for children with or without VUR (Table 3). Only 2 of the 5 children with grade IV VUR completed the study, and both had renal scarring at their follow-up scintigraphy.

**DISCUSSION**

This multicenter randomized trial compared a 10-day course of oral cefixime to a 4-day course of intravenous ceftriaxone treatment followed by a 6-day course of oral cefixime for the treatment of 1- to 36-month-old children encountering their first case of APN associated with renal damage, as determined by early scintigraphy. We did not find any difference between the 2 groups in the prevalence of renal scarring detected 6 to 8 months after the infection.

No currently available antibiotic therapy is able to prevent renal scarring after pyelonephritis. The frequencies of renal scarring in our treatment groups are comparable with those of previous trials, which reported renal scarring frequencies of 15% to 20% and 45% to 60%. However, it is not possible to conclude whether the oral treatment is noninferior because our study lacks sufficient statistical power.

Three previous prospective pediatric trials have been reported that compared oral treatment to sequential treatment with respect to the incidence of renal scarring detected by DMSA scintigraphy. We considered only those children with first-episode APN and an abnormal acute-phase scintigraphy in these studies. In the Hoberman et al study, 15 children of the 100 in the oral group with acute abnormal scintigraphy had renal scarring and 11 of 87 (12.7%) with the sequential treatment. In the Montini et al study, 26 of 96 (27.1%) children in the oral group and 33 of 100 in the sequential group had renal scarring. In the Neuhaus et al study, there were 18 of 64 children (28.1%) in the oral group and 22 of 55 (40%) in the sequential group who had definitive renal scarring.

Because high serum PCT concentrations have been reported to correlate with acute renal defects detected by early DMSA scintigraphy, we used serum PCT concentration to identify children who were at high risk for renal involvement. Because one of our inclusion criteria was a PCT value ≥0.5 ng/mL, 85.4% of the patients in our study had positive acute phase scintigraphies. In the 3 previous studies, 61.1%, 60.5%, and 63.3% of children, respectively, with febrile UTIs had abnormal acute scintigraphy.

Consistent with what has been previously reported, we found that serum PCT concentrations were significantly higher in children who developed scars than in those who had acute abnormalities but no definitive damage. For this reason, monitoring PCT levels in children afflicted with APN could help to identify those at risk for renal complications even in the absence of a suspected or documented uropathy.

All pathogens isolated in this study were *E coli*, which is usually the main pathogen isolated in UTI but not the only

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**TABLE 2 Renal Scarring**

<table>
<thead>
<tr>
<th></th>
<th>Oral Treatment</th>
<th>Standard Treatment</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (n = 119)</td>
<td>25/61 (41%)</td>
<td>26/58 (44.8%)</td>
<td>Risk difference = -3.8%</td>
</tr>
<tr>
<td>(95% CI: 28.7%–53.3%)</td>
<td>(95% CI: 32%–57.6%)</td>
<td>(95% CI: -21.9% to 13.9%)</td>
<td></td>
</tr>
<tr>
<td>PPA (n = 96)</td>
<td>16/62 (30.8%)</td>
<td>12/44 (27.3%)</td>
<td>Risk difference +3.5%</td>
</tr>
<tr>
<td>(95% CI: 18.3%–43.3%)</td>
<td>(95% CI: 14.1% to 40.5%)</td>
<td>(95% CI: -14.7% to +21.7%)</td>
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</tr>
</tbody>
</table>

**TABLE 3 Renal Scarring Depending on Age, Gender, and VUR**

<table>
<thead>
<tr>
<th></th>
<th>Oral Treatment</th>
<th>Standard Treatment</th>
<th>Overall</th>
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</thead>
<tbody>
<tr>
<td>(n = 52)</td>
<td>(n = 44)</td>
<td>(n = 96)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>12/37 (32.4%)</td>
<td>10/30 (33.3%)</td>
<td>22/67 (32.8%)</td>
</tr>
<tr>
<td>≥1 y</td>
<td>4/15 (26.7%)</td>
<td>2/14 (14.3%)</td>
<td>6/29 (20.7%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12/35 (34.3%)</td>
<td>7/30 (23.3%)</td>
<td>17/63 (27.0%)</td>
</tr>
<tr>
<td>Male</td>
<td>4/17 (23.5%)</td>
<td>5/14 (35.7%)</td>
<td>11/33 (33.3%)</td>
</tr>
<tr>
<td>VCGa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>14/40 (35.0%)</td>
<td>8/33 (24.2%)</td>
<td>22/73 (30.1%)</td>
</tr>
<tr>
<td>VUR</td>
<td>2/11 (18.2%)</td>
<td>4/11 (36.4%)</td>
<td>6/22 (27.3%)</td>
</tr>
</tbody>
</table>

* One child without renal scanning in the oral treatment group did not have VCG.
patients with a normal prenatal ultrasound and normal ultrasound exam at the time of APN diagnosis. This may explain why only 5 children in our study had high grade reflux (grades IV or V) and why, with this small number, renal scarring did not correlate with VUR.

In France, almost all units follow the 2007 Agence Française de Sécurité Sanitaire des Produits de Santé recommendations and treat APN in children with initial parenteral treatment followed by oral antibiotic.14 For this reason, it was difficult to include a sample size large enough to achieve the necessary level of statistical significance. In addition, 10 patients were not followed up, and 12 patients withdrew their consent. The high number of patients who dropped out of the study could reflect the unwillingness of parents and their children to participate in prospective clinical trials, especially when studies last several months and include procedures that are perceived as invasive.4 Such concerns considerably reduced the number of patients in the PPA.

CONCLUSIONS

Our results support the use of a completely oral cefixime treatment for initial episodes of APN involving a Gram-negative bacteria strain in infants and children aged 1 month to 3 years who are without urological abnormalities and without clinical hemodynamic impairment. This treatment can be proposed for children with serum PCT concentrations >0.5 ng/mL who are at high risk for renal involvement, as determined by acute-phase scintigraphy, and also for children who have lower PCT concentrations, despite their low risk for acute renal involvement. Oral treatment can facilitate outpatient management of young children with APN because it reduces cost, familial disruption, and nosocomial disease exposure.

ACKNOWLEDGMENTS

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