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Children with acute pyelonephritis need medical re-evaluation when home-treated with oral antibiotics.

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Abstract.

Aim: To investigate the efficacy and safety of home-treatment with oral piv-mecillinam or amoxicillin-clavulanate for children with acute pyelonephritis.

Methods: Children aged over 6 months diagnosed with culture confirmed pyelonephritis at Danish Paediatric Departments were home-treated with piv-mecillinam (tablets) or amoxicillin-clavulanate (liquid or tablets). Follow-up was performed by phone (second treatment day) and clinical review of the patients in hospital (day three).

Results: 418 children were included. In total, 333/418 (80%) responded well to the initial oral antibiotic treatment. 85/415 (20%) were changed to another oral antibiotic 47/418 (11%) or intravenous antibiotics 38/418 (9%) because of insufficient clinical improvement or bacterial resistance

Bacterial resistance similar for piv-mecillinam and amoxicillin-clavulanate: 4/74 (5%) versus 33/333 (10%), (p=0.22). Insufficient clinical improvement, despite no resistance, primarily occurred in children treated with piv-mecillinam: 16/74 (22%) versus 28/344 (8%), (p<0.001), and predominantly occurred in piv-mecillinam treated children <5 years: 7/20 (35%) versus 9/54 (17%), (p<0.05), potentially because of problems with piv-mecillinam tablets.

There were no deaths or cases of septicemia after start of initial oral antibiotics.

Conclusion: A home-treatment regime for pyelonephritis in children >6 months is safe, but during treatment clinical re-evaluation is required as in 20% of cases a change in treatment was necessary.

Key Notes

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- Oral antibiotics for pyelonephritis in children are commonly prescribed, but to our knowledge no home-treatment regimen with piv-mecillinam or amoxicillin-clavulanate has been evaluated.
- The home-treatment was successful, but clinical review during treatment is necessary as 20% of the children require adjustment of the treatment regime, 45% of these to intravenous antibiotics.
- Home-treatment with piv-mecillinam (tablets) was better for children aged 5 and above as compared to younger children.

Key Words: amoxicillin-clavulanate, home-treatment, paediatrics, piv-mecillinam, pyelonephritis

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Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in children. At the age of seven years, about 8% of girls and 2% of boys have been treated at least once for UTI (1). Acute pyelonephritis may result in significant morbidity and can cause permanent kidney damage. The optimum antibiotic regimen for acute pyelonephritis remains a matter of debate (2-8).

In Denmark the recommended treatment for children with pyelonephritis is intravenous antibiotics for 3-5 days followed by 5-7 days of oral antibiotics with a total treatment length of 10 to 14 days (2,9). There are clear advantages to treatment with oral antibiotics at home, both for patients and caregivers as well as a significant socioeconomic savings. Oral antibiotics for acute pyelonephritis have been shown to be safe and effective when children with sepsis or known urological abnormalities were excluded (10-13). These studies used third generation oral cephalosporins which are not available in Denmark and the children were either hospitalized or visited hospital to achieve the antibiotics (10,11,13). To our knowledge no study has evaluated the use of piv-mecillinam tablets, and only one has evaluated amoxicillin-clavulanate (12).

Before initiating this clinical study, we analysed the antimicrobial susceptibility of uropathogenic bacteria in urine isolates from 378 children younger than 16 years at a hospital in Copenhagen, Denmark. For both piv-mecillinam and amoxicillin-clavulanate the resistance rates of the proved uropathogens were 7% in children over six months of age (14).

We included children from the age six months upwards, as the risk of bacteraemia in pyelonephritis is higher with younger age. In infants below two months up to 22% suffer from bacteraemia compared to 3% in children aged two to 36 months (15). Moreover, in children older than six months of age, none had bacteraemia in contrast to 8% for those aged 3.1-6.0 months with even higher rates for children below this age (16). A third study only reported bacteraemia in 1/365 (0.3%) children aged six months or older treated with oral antibiotics for pyelonephritis (10).

The purpose of this prospective multicentre study was to evaluate whether children aged over six months with acute pyelonephritis could be effectively and safely treated with oral piv-mecillinam or amoxicillin-clavulanate at home when clinical re-evaluation was performed at hospital during treatment.

Material and methods

Study design

The nephrology working-party of the Danish Paediatric Society designed a protocol for home-treatment of pyelonephritis with oral piv-mecillinam or amoxicillin-clavulanate. All paediatric departments in Denmark were invited to participate. We included patients from the paediatric emergency ward, diagnosed with pyelonephritis. The definition of pyelonephritis followed the Danish guidelines. The diagnose was based on symptoms including fever above 38.0 Celsius in children above 24 months while children younger than 24 months were included with symptoms as reduced feeding, stomach pain, unwell appearance, but fever was not a mandatory symptom (2). For both age groups the diagnosis included a significant growth of uropathogenic bacteria. Leukocyturia was not an inclusion criterion, based on the Danish guidelines (2), since some children without leukocyturia especially the younger might still have a UTI.
The parents gave informed consent to home-treatment.

The following patients were excluded; age below 6 months, sepsis defined clinically by the clinician in each of the 11 centers based on hypotension, poor capillary refill, tachycardia and toxic appearance, known urological anomalies, antibiotics prior to urine collection, elevated serum creatinine at admission, allergy to penicillin, phenylketonuria, impaired liver function, known immunodeficiency, unable to take oral medication due to vomiting and inadequate fluency in Danish or English language. Figure 1. Furthermore, some departments excluded patients previously treated for pyelonephritis. The criteria of exclusion were broad as the children were antibiotic treated at home solely with observation by their parents.

The home-treatment protocol demanded that the parents contacted the Department of Paediatrics if the child was unwell, vomited or was unable to take the prescribed antibiotics. To ensure clinical response, a nurse contacted the family by phone on the second day of treatment, and the child was re-evaluated at the hospital on day three.

Urine was collected either by suprapubic bladder aspiration (children below two years only), by catheterization (girls only) or by clean midstream urine, ideally twice.

For suprapubic bladder aspiration any growth of uropathogenic bacteria was considered significant. For catheterization growth of $\geqslant$1000 colony-forming units/ml (cfu/ml) of a single uropathogen was considered significant, and in clean midstream urine samples, a positive urine culture was defined as growth of $\geqslant$10,000 cfu/ml of a single uropathogen (17). *Esherichia coli (E. coli)* was noted and interpreted as one group, all other uropathogenic bacteria were grouped as *non-E. coli.* Growth of *non-hemolytic streptococci*, *Corynebacterium species* and all *coagulase-negative staphylococci*, except *Staphylococcus saprophyticus*, were excluded as these bacteria were interpreted as being contamination from skin or mucosa (17). Urine samples with more than one bacterium were interpreted as contamination (2,17). Patients with such growth were excluded from further analysis.

Antibiotic treatment was administered three times daily for 10 days. Total daily dose for piv-mecillinam was 20-40 mg/kg/day and for amoxicillin-clavulanate 40-50 mg amoxicillin /kg/day. In Denmark piv-mecillinam is available only in tablet form whereas amoxicillin-clavulanate is available both as oral syrup and tablets. Choice of antibiotics was made by the clinician.

The patients were changed to alternative antibiotics in cases of insufficient clinical improvement including persistent fever 48 hours after start of antibiotic treatment, persistent clinical ill appearance or significant increase in C-reactive protein. The patients were switched to alternative antibiotics on day one to three depending on the individual evaluation, either when the family contacted the hospital due to persistent fever, deterioration, difficulties in taking the medication, vomiting or other worries, or when the nurse called the family on day two, or on day three during clinical re-evaluation.

The number of patients with insufficient clinical improvement and resistance was noted. Resistance was determined from disk diffusion according to either EUCAST methodology or Vitec 2 system (18). Isolated bacteria not tested for amoxicillin-clavulanate were excluded in the figures for resistance. In cases where there was microbiological laboratory resistance of the isolated bacteria to the antibiotic, but adequate clinical effect the patients were not classified with resistance.

An ultrasound of the kidneys and urinary tract was performed within the first months after the diagnosis of pyelonephritis. Dilated renal pelvis was defined as an anterior-posterior diameter of at least 10 mm, and a difference in the length of the kidneys of more than one cm was categorised as an anomaly (19). We could have repeated the ultrasound to see if the difference in kidney size depended on swelling from the UTI or congenital hypoplasia, but in this multicenter study we unfortunately did not have data on that.

Some departments additionally performed renal scintigraphy either a Technetium-99m mercaptoacetyltriglycine renography (MAG3) or a technetium-99m dimercaptosuccinic acid scintigraphy (DMSA) after the infection. Unilateral impaired renal function was defined as a renal differential function of less than 40%, based on the Danish guidelines and the European Society of Paediatric Urology (ESPU) guidelines (19).

Outcome measures

The primary outcome was efficacy of the initial treatment, measured as the number of children who successfully completed the initial antibiotic treatment regimen.

Secondary outcomes were efficacy of the home-treatment, measured as the number of children who successfully completed oral antibiotics for pyelonephritis at home.

S*afety* was evaluated as the number of deaths or development of septicemia after start of initial oral antibiotics.

Statistical analysis

Continuous variables are presented as medians with ranges, differences between groups were tested with Mann Whitney U test. Categorical variables are presented as frequencies and between groups differences were tested by Fischer's exact test or uncorrected chi square test. Tests were generally performed as double-sided analyses. A p-value below 0.05 was considered statistically significant.

The analysis was performed in the Internet-based statistics program Open Source Epidemiologic Statistics for Public Health (www.OpenEpi.com) which was updated in 2013, Social Science Statistics (www.socscistatistics.com) and SPSS version 25.0 for windows (IBM, Chicago, IL).

Ethics

The Study was conducted according to the Helsinki II Declaration and approved by the Danish Data Protection Agency (J.no. 2007-58-0006).

Results

Included patients

The protocol was applied in 11 out of 18 Danish paediatric departments between 1st October 2014 and 31st December 2015. Data from 644 children was received: 418 children (365 girls, 87%) met the inclusion criteria. Median age was 2.2 years (range 6 months to 16.2 years). The age of the boys was median 1.7 years (range 0.5-13.8) and the age of the girls was median 2.4 years (range 0.5-16.2 years), (p=0.10). Figure 1.

Results of urine culture

In total 51 children (12%) had urine samples obtained by suprapubic aspiration, 252 (60%) by two clean midstream urine samples and in 10 girls (2%), urine was obtained by catheterization. The remaining patients had one clean midstream urine collected 105/418 (25%).

E. coli was the most common uropathogen identified in the isolates of 386 patients (92%). The identified *non-E. coli bacteria* were: *Klebsiella* species*, Proteus mirabilis, Citrobacter, Enterobacter* and *Pseudomonas aeruginosa species* grouped together (n=20*), Staphylococcus saphrophyticus*, *Streptococcus agalactiae* and *aerococcus* species (n=9) and *enterococcus* species (n=3).

Resistance to the prescribed antibiotic was reported for 39/418 (9%) of the samples. However, in two girls, this was of no clinical significance as they responded clinically to the initial antibiotics. In 11 girls the samples were not tested for resistance for amoxicillin-clavulanate, and these patients were excluded from the resistance analysis. Therefore 37/407 (9%) of the urine samples were resistant to the prescribed antibiotic; in 4 (5%) cases to piv-mecillinam and in 33 (10%) to amoxicillin-clavulanate, (p=0.22). *C*hildren with *E. coli* in the isolates had a lower rate of resistance than those with *non-E. coli* 29/386-11 (8%) versus 8/32 (25%), (p=0.001). Boys presented more often with *non-E. coli* bacteria in the urine samples and with a higher risk of

resistance than girls, 14/53 (26%) versus 18/365 (5%), (p<0.001) and 9/53 (17%) versus 28/354 (8%), (p<0.05).

Treatment with oral antibiotics

Initially, 74/418 (18%) of the children were treated with piv-mecillinam and 344/418 (82%) were treated with amoxicillin-clavulanate, Figure 2, Table 1. The patients who started treatment with piv-mecillinam were older and had a lower c-reactive protein compared to those treated with amoxicillin-clavulanate, (p<0.001) and (p<0.05), Table 1.

Treatment efficacy and safety

In 80% (333/418) of the children treatment with the initial antibiotic was successful; 54/74 (73%) for piv-mecillinam and 279/344 (81%) for amoxicillin-clavulanate, (p=0.12), Figure 2, Table 1.
In total 44/85 (52%) of the children were switched to alternative antibiotic treatment regimens due to insufficient clinical improvement, despite susceptibility of the isolated bacteria to the initial antibiotic. This was more common in children treated with piv-mecillinam compared to amoxicillin-clavulanate 16/74 (22%) versus 28/344 (8%), (p<0.001), Table 1, and it primarily occurred in piv-mecillinam treated children younger than 5 years: 7/20 (35%) versus 9/54 (17%), (p<0.05, one-sided). When analyzing data for the 290 children aged less than 5 years, the risk of insufficient clinical improvement, despite no resistance, was higher in those treated by piv-mecillinam than by amoxicillin-clavulanate 7/20 (35%) versus 21/270 (8%), (p<0.0001). In contrast, when analyzing data for the 128 children aged 5 years and above, the risk of insufficient clinical improvement, despite no resistance, was equal in those treated by piv-mecillinam and by amoxicillin-clavulanate 9/54 (17%) versus 7/74 (10%), (p=0.22).

The secondary outcome, efficacy of home-treatment with oral antibiotics regardless of whether there was a need to change to other oral antibiotics was 380/418 (91%): 64/74 (86%) for initial piv-mecillinam and 316/344 (92%) for initial amoxicillin-clavulanate, (p=0.15), Figure 2.

In total, 38/418 (9%) children were changed to intravenous antibiotics: 10/74 (14%) of children who were initially treated with piv-mecillinam and 28/344 (8%) of children initially treated by amoxicillin-clavulanate (p=0.15). The reasons for switching to intravenous treatment were: resistance (3 patients), insufficient clinical improvement despite no resistance (17 patients), vomiting (8 patients), positive blood culture and lack of clinical improvement (4 patients), poor compliance (5 patients) and increasing plasma creatinine (1 patient). All these 38 children underwent hospitalization.

The children who were changed from the first-choice oral antibiotic had a tendency towards more *non-E. coli* bacteria in urine cultures (p=0.052) and had more often previously had pyelonephritis (p=0.056) than those who completed treatment with the initial oral antibiotic, but differences were not statistically significant, Table 2.

Regarding safety, home-treatment with oral antibiotics was considered safe as no patients died or developed septicemia.

Urological anomalies

Renal ultrasound was abnormal in 39/405 (10%), and renal scintigraphy (MAG3 or DMSA) was abnormal in 37/275 (14%) of the children, Table 2. Unilateral impaired renal function was seen in 21/275 (8%) and renal scarring in 19/275 (7%) of the children.

Non-E. coli in the urine samples were identified more often in children with abnormal renal scintigraphy: 7/24 (29%) versus 30/251 (12%), (p=0.042), but were seen with equal frequency in those with abnormal and normal renal ultrasound: 4/30 (13%) versus 35/375 (9%), (p=0.48).

No associations were found between urological anomalies and need for change of the initial antibiotic. No increase in risk for development of renal scaring was observed in those who did not initially received adequate antibiotic treatment, Table 2.

Discussion

We present here evidence that oral antibiotic treatment, at home, of children with acute pyelonephritis is effective and safe. It is however essential that the children are clinically re-evaluated during the course of the treatment, as 20 % of the children required a change from the initial antibiotic regime.

In Denmark, parenteral antibiotic treatment for pyelonephritis in children has been traditionally recommended (2). Recent international studies (10-13) have shown oral antibiotics to be comparable in terms of efficacy, but these studies have included hospitalisation of the child or antibiotic administration every day via emergency departments. This prospective multicentre home-treatment study proves an efficient and safe treatment regimen for pyelonephritis in which 91% of the children successfully completed an oral antibiotic course. Other studies have reported that during home-treatment with oral antibiotics for pyelonephritis close communication with the families of such children is indicated (21,22). A Belgian study of 82 patients showed that 21% of the children home-treated with cefuroxime-axetil for pyelonephritis required hospitalization for parenteral antibiotics (22). This is in line with our findings of 20% requiring change to another oral or intravenous antibiotic. In our study this was primarily the result of insufficient clinical improvement and was more common in patients treated with piv-mecilliam than with amoxicillin-clavulanate. This was especially the case in children younger than 5 years of age, whereas no difference was exhibited in children aged at least 5 years. In Denmark piv-mecillinam is available as tablets only, meaning that patients aged < 5 years have an increased risk of treatment failure despite bacterial susceptibility, possibly due to difficulties with tablet administration and adherence to treatment. An additional factor may be that some of these children received crushed tablets of piv-mecilliam, with possibly inadequate pharmacokinetic profiles. The efficacy of piv-mecillinam has previously been reported in children aged 0.5 to 14 years but in that study, the youngest

children received piv-mecillinam suspension (23). These findings prompt us to suggest that if piv-mecillinam tablets are not swallowed there is a risk of treatment failure. This is in line with the Norwegian pediatric recommendation (24). In Denmark piv-mecillinam is the antibiotic of choice for treatment of lower urinary tract infection in adults (26), but only 2% of all piv-mecillinam prescriptions are to children younger than 14 years of age (25).

Resistance to the proven uropathogen was seen in 9% of patients; 5% to piv-mecillinam and 10% to amoxicillin-clavulanate. Our finding of 10% resistance of uropathogens to amoxicillin-clavulanate may indicate a higher frequency of resistance than previously reported (6% in 2010–2013) (14). In Italy in 2000-2005, resistance to amoxicillin-clavulanate in children treated for pyelonephritis was 6% (12), but in 2007-2009, for children, it was 6% of outpatients and 10% of inpatients (27). In Greece from 2010 to 2015, 12% resistance of *E. coli* to amoxicillin-clavulanate was reported in children treated for UTI (28). It has been suggested that a resistance rate lower than 10% is acceptable for empirical treatment (15,29). The present finding of 10% resistance to amoxicillin-clavulanate highlights the importance of a close medical contact when children are initially home-treated with amoxicillin-clavulanate. In contrast, a low rate of resistance to piv-mecillinam was observed in this study and in studies from other countries which also have a high piv-mecillinam usage (29).

Boys had a higher risk of resistance to the isolated bacteria than girls, due to higher frequency of non-*E.coli* bacteriuria. This finding is accordance is in accordance with the literature (14,19).

It was not possible to identify predictors for those children requiring hospitalization and intravenous treatment, but children with a previous UTI had a tendency to be changed to intravenous antibiotics. In general, oral antibiotic treatment is not recommended for pyelonephritis in children with known urological anomalies (3,5,6). In Denmark all pregnant women are offered antenatal ultrasound (30) and we excluded patients with known urological diagnoses. This might explain the rather low incidence of ultrasound abnormalities (10%) in our cohort.

The finding of *non-E. coli* bacteriuria was more common in children with urological anomalies: 29% in those with abnormal renal scintigraphy and 13% in those with abnormal ultrasound. This is in line with a frequency of 22% *non-E. coli* bacteriuria in patients with urological diagnoses in a previous Danish cohort study including 472 children treated for first episode of pyelonephritis without previously known urological anomalies (19).

All the children were diagnosed in hospital. Treating children with pyelonephritis at home with oral antibiotics reduced the number of in-patient stays to 9%, as only 9% of children were switched to intravenous antibiotics and therefore hospitalized. Moreover, in contrast to the previous hospital admission we had one telephone consultation and one outpatient consultation. For both the individual families concerned and the health care system it was beneficial that oral antibiotic treatment at home avoided the need for hospitalization in 91% of the children.

Strengths and limitations

This study is the first prospective multicenter cohort study of treatment at home with piv-mecillinam or amoxicillin-clavulanate in children with acute pyelonephritis.

It is a limitation that the choice of antibiotic treatment was not blinded and randomized meaning that comparing the efficacy of the two antibiotics is not optimal. Moreover, some departments treated children below 5 years of age with tablets of piv-mecillinam, which may have lead to a higher risk of treatment failure in those children.

Conclusion

Oral home-treatment of acute pyelonephritis with piv-mecillinam or amoxicillin-clavulanate is effective and safe and can minimize hospitalization of children. Clinical review during treatment is necessary as 20% of the children require adjustment of the treatment regime, 45% of these to intravenous antibiotics.

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Complete list of abbreviations used

AB: Antibiotics

MAG3: Technetium-99m mercaptoacetyltriglycine renography

DMSA: technetium-99m dimercaptosuccinic acid scintigraphy

UTI: Urinary Tract Infection

E. coli: Escherichia coli

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The authors report no conflict of interest in this study.

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Table 1

Characteristics of 418 patients treated for pyelonephritis, classified by the initial oral antibiotic.

	Initially treated by piv-mecillinam	**Initially treated by amoxicillin-clavulanate**	**p-value**
Number (%)	74/418 (18%)	344/418 (82%)	
Age median, (range), years	6.8 (0.7-15.2)	1.9 (0.5-16.2)	<0.0001
Girls	66/74 (89%)	299/344 (87%)	0.76
C-reactive protein, mg/l	66 (3-229)	76 (0-340)	0.048
Escherichia coli	66/74 (89%)	320/344 (93%)	0.26
Fulfilled the initial antibiotics	54/74 (73%)	279/344 (81%)	0.11
Fulfilled treatment with first or second-line oral antibiotics	64/74 (86%)	316/344 (92%)	0.15
Fulfilled treatment with intravenous antibiotics	10/74 (14%)	28/344 (8%)	0.15
Resistance	4/74 (5%)	33/333 (10%)	0.22
Insufficient clinical improvement, despite no resistance	16/74 (22%)	28/333 (8%)	0.0006

Table 2

Characteristics of the 418 patients treated for pyelonephritis with oral antibiotics classified according to completion of the initial oral antibiotic course.

	Switched from the initial oral antibiotic	Treated by initial oral antibiotics	P-value
Number	85	333	
Age, years	2.0 (0.5-16.2)	2.3 (0.5-15.2)	0.43
Boys	14/85 (16%)	39/333 (12%)	0.24
C-reactive protein median (range), mg/l	75 (2-307)	72 (0-340)	0.96
Previous treated for pyelonephritis	16/85 (19%)	37/333 (11%)	0.056
Escherichia coli	74/85 (87%)	312/333 (94%)	0.052
Ultrasonographic anomalies:	10/81 (12%)	29/324 (9%)	0.35
- Hydronephrosis	5, 1 also with dilated ureter	11, 3 also with dilated ureter	0.25
- Dilated ureter	0	2	-
- Duplex kidney	2	7	0.87
- At least 1 cm difference in kidney size	2	8	>0.999
- Bilateral hypoplastic kidneys	0	1	-
- Benign tumour in the bladder	1	0	-
Scintigraphy anomalies:	7/55 (13%)	30/220 (14%)	0.86
- Impaired unilateral renal function	4/55 (7%)	17/220 (8%)	0.91
- A renal scar	4/55 (7%) *	15/220 (6%) #	0.91
- Dilated ureter	0	1/55 (2%)	-
- Duplex kidney	0	1/55 (2%)	-

* One patient had both impaired unilateral renal function and a renal scar

Four patients had both impaired unilateral renal function and a renal scar