

- Wilson JMG, Jungner G. *The principles and practice of screening for disease*. WHO Public Health papers. Geneva: World Health Organization, 1968:34.
- Majeed A, Moser K, Carroll K. Trends in prevalence of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. *Heart* 2001;86:284-8.
- Morgan S, Mant D. Randomised trial of two approaches to screening for atrial fibrillation in UK general practice. *Br J Gen Pract* 2002;52:373-80.
- Somerville S, Somerville J, Croft P, Lewis M. Atrial fibrillation: a comparison of methods to identify cases in general practice. *Br J Gen Pract* 2000;50:727-9.
- Wheeldon NM, Tayler DI, Anagnostou E, Cook D, Wales C, Oakley GDG. Screening for atrial fibrillation in primary care. *Heart* 1998;79:50-5.
- Marjoram J, Strachan R, Allan A, Allan E. Screening for colorectal cancer a general practice based study. *Br J Gen Pract* 1996;46:283-6.

Accepted: 29 June 2007

Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial

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BMJ 2007;335:386-8
doi:10.1136/bmj.39244.692442.55

This article is an abridged version of a paper that was posted on bmj.com on 4 July 2007. Cite this version as: *BMJ* 4 July 2007, doi:10.1136/bmj.39244.692442.55 (abridged text, in print: *BMJ* 2007;335:386-8).

ABSTRACT

Objective To compare the efficacy of oral antibiotic treatment alone with treatment started parenterally and completed orally in children with a first episode of acute pyelonephritis.

Design Multicentre, randomised controlled, open labelled, parallel group, non-inferiority trial.

Setting 28 paediatric units in north east Italy.

Participants 502 children aged 1 month to <7 years with clinical pyelonephritis.

Intervention Oral co-amoxiclav (50 mg/kg/day in three doses for 10 days) or parenteral ceftriaxone (50 mg/kg/day in a single parenteral dose) for three days, followed by oral co-amoxiclav (50 mg/kg/day in three divided doses for seven days).

Main outcomes measures Primary outcome was the rate of renal scarring. Secondary measures of efficacy were time to defervescence (<37°C), reduction in inflammatory indices, and percentage with sterile urine after 72 hours. An exploratory subgroup analysis was conducted in the children in whom pyelonephritis was confirmed by dimercaptosuccinic acid (DMSA) scintigraphy within 10 days after study entry.

Results Intention to treat analysis showed no significant differences between oral (n=244) and parenteral (n=258) treatment, both in the primary outcome (scarring scintigraphy at 12 months 27/197 (13.7%) v 36/203 (17.7%), difference in risk -4%, 95% confidence interval -11.1% to 3.1%) and secondary outcomes (time to defervescence 36.9 hours (SD 19.7) v 34.3 hours (SD 20), mean difference 2.6 (-0.9 to 6.0); white cell count $9.8 \times 10^9/l$ (SD 3.5) v $9.5 \times 10^9/l$ (SD 3.1), mean difference 0.3 (-0.3 to 0.9); percentage with sterile urine 185/186 v 203/204, risk difference -0.05% (-1.5% to 1.4%)).

Similar results were found in the subgroup of 278 children with confirmed acute pyelonephritis on scintigraphy at study entry.

Conclusions Treatment with oral antibiotics is as effective as parenteral then oral treatment in the management of the first episode of clinical pyelonephritis in children.

Trial registration Clinical Trials NCT00161330.

INTRODUCTION

Published guidelines for the treatment of acute pyelonephritis recommend initial treatment with a parenteral third generation cephalosporin followed by oral antibiotics.¹⁻³ A Cochrane review found no significant differences in the risk of persistent renal damage between initial intravenous (three to four days) followed by oral treatment and completely intravenous treatment (seven to 14 days).³ Only one previous randomised controlled trial compared oral treatment (cefixime) only with antibiotics started parenterally.⁴ There was no significant difference between the two groups in terms of renal scarring at six months (1.45, 95% confidence interval 0.69 to 3.03). Hoberman et al expressed some concern regarding the low rate of scarring in both groups in the study compared with the rates reported elsewhere.⁴ Furthermore, 90% of children studied were girls and the mean age of the children was 8 months.

We conducted a non-inferiority randomised controlled trial to determine whether an entirely oral treatment with co-amoxiclav is therapeutically similar to an initial parenteral treatment with ceftriaxone followed by oral co-amoxiclav in children with clinical acute pyelonephritis. Oral treatment is easier to use and does not require admission to hospital, leading to reduced costs.

METHODS

The study was a randomised controlled, multicentre, open labelled, parallel group, non-inferiority trial. It was performed from June 2000 to July 2005 at 28 paediatric units.

Diagnosis—Recruited children were aged from 1 month to <7 years and had a clinical diagnosis of acute pyelonephritis at presentation according to urinalysis (two concordant consecutive test results with white cell counts $\geq 25/\mu l$ and urine culture (two

concordant consecutive tests with growth of only one micro-organism $\geq 100\,000$ colony forming units/ml). Children also had to have at least two of fever $\geq 38^\circ\text{C}$; raised inflammatory indices in the first 48 hours (erythrocyte sedimentation rate or C reactive protein or both); and neutrophil count above the normal values for age. All recruited children were admitted to hospital and remained there until their temperature was normal or at least three days. The localisation of infection was confirmed by an acute positive result on dimercaptosuccinic acid (DMSA) scintigraphy in those children who underwent the procedure within 10 days after the start of antibiotic treatment.

Inclusion and exclusion criteria—All children had to have had normal findings on prenatal ultrasonography, no history of acute pyelonephritis, and no documented renal or urological abnormalities. We excluded children with severe clinical sepsis, dehydration, and vomiting, which precluded administration of oral antibiotics; ongoing antibiotic treatment; allergy to the study drugs; creatinine clearance ≤ 70 ml/min/1.73 m².

Interventions—After recruitment, children were allocated to oral treatment with co-amoxiclav 50 mg/kg/day in three doses for 10 days (new treatment) or initial parenteral treatment with ceftriaxone 50 mg/kg/day in a single dose for three days, followed by oral co-amoxiclav 50 mg/kg/day in three doses for seven days (standard treatment³). We modified treatment in children whose health deteriorated in the 48 hours after the start of treatment; those with persistent fever ($>38^\circ\text{C}$) in the 72 hours after the start of treatment; and those with intolerance or an adverse reaction to the drugs used. Haematological inflammatory indices, urinalyses, and urine culture were repeated on the third day of treatment.

Imaging studies—Ultrasonography and scintigraphy were planned no later than 10 days after the start of antibiotic treatment. After treatment was completed, children remained on antibiotic prophylaxis until voiding cystography was carried out (within two months). If children had a positive result on

scintigraphy for acute pyelonephritis we scheduled a repeat scan after one year to detect any renal scarring. Two nuclear physicians, blinded to the test results, interpreted the scans independently and resolved discrepancies by discussion.

Outcome measurements—Our primary end point was the rate of renal scarring after 12 months. The secondary outcome was the efficacy of antibiotic treatment in the short term: time to defervescence (axillary temperature $<37^\circ\text{C}$), reduction in inflammatory indices, and percentages with sterile urine 72 hours after the start of treatment. We carried out an exploratory subgroup analysis of primary and secondary outcomes in the group of children with pyelonephritis confirmed by scintigraphy performed within 10 days after the start of antibiotic treatment. We compared the safety and acceptability of treatment in terms of the rate of discontinuation of treatment and the incidence of side effects.

Randomisation—Randomisation was stratified for sex and age (<2 years *v* ≥ 2 years) (see bmj.com). We could not blind group assignment because of the different routes of administration of the drug.

Statistical analysis—Around 15% of children with acute pyelonephritis treated with parenteral antibiotics, show measurable renal scars 12 months after infection. We therefore considered that an upper confidence limit of 25% for the new (oral) treatment would indicate non-inferiority. We adopted 10% as the margin of equivalence. We therefore required 220 children per group, with 90% power and 5% *a* error for a one tailed test (see bmj.com).

RESULTS

Patients

A total of 502 children were recruited from June 2000 to June 2004. Follow-up was completed in July 2005. Children were randomised to either oral antibiotic (new treatment, n=244) or initial parenteral antibiotic (standard treatment, n=258). We analysed data from all the 502 randomised children (intention to treat analysis).

Four hundred children completed the trial and were measured for renal scarring—the primary outcome (223 underwent scintigraphy at 12 months; 177 were considered to have negative results at 12 months because they had negative results at study entry). After they completed antibiotic treatment, 102 (20.3%) patients were lost to follow-up with no significant difference between the groups. Of the 223 patients who underwent the renal scan at 12 months, scintigraphy at entry had confirmed pyelonephritis in 207 and was negative in 16. These 16 were scanned at 12 months for reasons other than the protocol and the scan result was negative.

There was no significant difference in adherence to protocol for scintigraphy at entry in the two groups (see bmj.com). Of the 438 patients who underwent scintigraphy within 10 days, in 278 (135/216 in the new treatment group and 143/222 in standard treatment group) the results confirmed acute pyelonephritis,

Primary and secondary outcomes according to treatment in the 502 randomised children according to allocation to new treatment (oral co-amoxiclav) or standard treatment (intravenous ceftriaxone followed by oral co-amoxiclav). Figures are means (SD) unless specified otherwise

Parameter	New treatment (n=244)	Standard treatment (n=258)	Mean difference (95% CI)
Short term outcomes			
Time to defervescence (hours)	36.9 (19.7) (n=241)	34.3 (20) (n=253)	2.6 (-0.9 to 6)
White cell count ($\times 10^9/l$)*	9.8 (3.5) (n=230)	9.5 (3.1) (n=243)	0.3 (-0.3 to 0.9)
Neutrophils ($\times 10^9/l$)*	3.0 (2.2) (n=207)	2.8 (1.9) (n=217)	0.2 (-0.2 to 0.6)
Erythrocyte sedimentation rate (mm in first hour)*	50.8 (32) (n=170)	52.6 (27.9) (n=168)	-1.8 (-8.2 to 4.7)
C reactive protein (mg/l)†	9.3 (20.9) (n=235)	8.2 (15.4) (n=251)	1.1 (-2.6 to 4.1)
Sterile urine	185/186 (99.45%)	203/204 (99.5%)	-0.05% (-1.5% to 1.4%)
Primary outcome			
Scar on renal scan at 12 months	27/197 (13.7%)	36/203 (17.7%)	-4% (-11.1% to 3.1%)

*Parameters obtained 72 hours after start of antibiotic treatment.

†Ratio between obtained value and upper limit of normal reference values for each laboratory.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Numerous studies have compared various parenteral antibiotic regimens for acute pyelonephritis in children

The only randomised controlled trial examining exclusive oral antibiotic treatment was carried out in an unusual population, with a strong female bias, and a disproportionately high incidence of vesicoureteral reflux

WHAT THIS STUDY ADDS

Treatment with oral antibiotics alone is not inferior to parenteral followed by oral treatment in the management of acute pyelonephritis in young children

Implementation of oral therapy could reduce costs and stress of admission to hospital in children

and these children constituted the population for the subgroup analysis.

Escherichia coli was the pathogen responsible in 94.4% (436/462) of confirmed urine cultures that showed bacteria growth. Bacterial resistance to protocol antibiotics was 6% (25/407) with co-amoxiclav and <1% (3/343) with ceftriaxone.

Outcomes

Scarring on scintigraphy at 12 months was not significantly different between the two groups (table). The subgroup analysis confirmed that the oral treatment was not inferior: 26/96 (27.8%) *v* 33/100 (33.0%); risk difference -5.8%, -18.7% to 6.9%. We found similar results when we counted all patients lost to follow-up in both groups as having a scar at 12 months (risk difference -4.9%, -13.1% to 3.3%).

There were no significant differences between the two treatment groups for the secondary outcomes (see bmj.com). The duration of hospital stay was similar in both groups (5.17 and 5.05 days).

Adverse effects

Fifteen children experienced minor side effects with initial treatment with co-amoxiclav; only 10 required a change of antibiotic. Three children experienced minor side effects with ceftriaxone that did not require change of treatment.

DISCUSSION

According to our definition of non-inferiority, this randomised controlled study in 502 young children with acute pyelonephritis shows that oral antibiotic treatment alone is as effective as initial parenteral treatment followed by oral. The two treatments were equivalent in terms of our primary outcome (renal scar rate) and the short term outcomes (time to defervescence, reduction in inflammatory indices, percentage with sterile urine). These results were found in children of both sexes, aged less than 7 years.

The results were found with an intention to treat analysis, which included children who started antibiotic treatment before a scintigraphic diagnosis of acute pyelonephritis, which represents the routine clinical scenario; the doctor in charge has to decide to start antibiotic treatment in a febrile child with a positive

result on urine dipstick testing. We confirmed our results in the subgroup analysis of children with the clear localisation of infection by renal scan—that is, those children with the most severe infections.

Strengths and weaknesses

A relatively high number of children were lost at the 12 month follow-up (102/502). Nevertheless, our study maintains its power in ascertaining the non-inferiority of the oral treatment, given the higher number of children enrolled and the fact that the numbers lost to follow-up were similar in both groups.

Comparison with other studies

One other study in the United States has examined the exclusive use of oral antibiotics.⁴ The population differed in terms of age, sex, and concomitant rate of urological abnormality. Our population included children up to the age of 7, the proportion of girls was more balanced in our study, and we had a more typical proportion of children with vesicoureteric reflux (21% *v* 38%). The US study also had a low scarring rate of 15% in children⁴ compared with 30% in our study, which is more usual. This finding is also inconsistent with the higher rate of vesicoureteric reflux in the US study (a recognised risk factor for renal scarring). The role of genetic variability could differ between the Italian and the US population.⁵ Time to defervescence was considerably shorter in the US study, which is difficult to explain.

Conclusions

In the management of the first diagnosed febrile urinary tract infection in children without urological abnormalities, an exclusive oral treatment is a reasonable option: the greater ease of oral treatment may facilitate care out of hospital and therefore have the potential to reduce costs and discomfort to children and their families.

We thank all the members of IRIS (Italian Renal Infection Study Group in children) who made the performance of this study possible. We particularly thank Daniela Gobber (epidemiologist) who died this year. We also thank Jennifer Hartwig, Ian Hewitt, and Federica Fregonese for their help in the preparation of the manuscript, Andrea Ponzoni for statistical analysis, and Roberto Buzzetti for epidemiological advice. The names of participants of the IRIS1 study are on bmj.com.

Contributors: See bmj.com.

Funding: Region of Veneto (research project 40/01) and association Il Sogno di Stefano (Stephen's Dream).

Competing interests: None declared.

Ethical approval: Ethics committees of each participating centre approved the study protocol.

- 1 Tolkoﬀ-Rubin NE, Cotran RS, Rubin HR. In: Brenner BM, ed. *The kidney*. 6th ed. Philadelphia, PA: WB Saunders, 2000:1449-508.
- 2 Working Group of the Research Unit, Royal College of Physicians. Guidelines for the management of acute urinary tract infection in childhood. *J R Coll Phys Lond* 1991;25:36-42.
- 3 Bloomeld P, Hodson EM, Craig JC. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev* 2005;(1):CD003772.
- 4 Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics* 1999;104:79-86.
- 5 Jahnukainen T, Chen M, Celsi G. Mechanisms of renal damage owing to infection. *Pediatr Nephrol* 2005;20:1043-53.

Accepted: 17 May 2007