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ORIGINAL ARTICLE

A systematic review of randomised clinical trials for oral antibiotic treatment of acute pyelonephritis

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Abstract

There is increasing resistance to the oral antibiotics currently recommended for the treatment of pyelonephritis, and increased healthcare costs are associated with the reliance on alternative intravenous agents. We, therefore, performed a systematic review of randomised controlled trials to determine the clinical efficacy and safety of oral antibiotics for the treatment of pyelonephritis in adults. A search of four major medical databases (MEDLINE, Embase+ Embase classic, CENTRAL and Cochrane Database for Systematic Reviews) in addition to manual reference searching of relevant reviews was conducted. Clinical cure and adverse event rates were reported, and trial quality and bias were assessed. A total of 277 studies were reviewed; five studies matched all eligibility criteria and were included. Antibiotics included were cefaclor, ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, loracarbef, norfloxacin, rufloxacin and trimethoprim-sulfamethoxazole. In included studies, the clinical success of the outpatient treatment of pyelonephritis by cefaclor, ciprofloxacin and norfloxacin at 4 to 6 weeks was comparable at between 83 to 95%. Relatively high rates of adverse events were noted in a trial of ciprofloxacin (24%) and trimethoprim-sulfamethoxazole (33%). Significant heterogeneity between all aspects of the trial designs was identified, with all studies having a potential for bias. This review demonstrates a need for high-quality clinical trials into the oral antibiotic treatment of pyelonephritis, with more consistent designs and reporting of outcomes. There are data to support further research into oral norfloxacin and cefaclor for the outpatient treatment of pyelonephritis in adults.

Keywords Pyelonephritis · Urinary tract infection · Antibiotic · Resistance · Oral

Introduction

Pyelonephritis is a bacterial infection of the renal pelvis and kidney. It is a life-threatening infection that can lead to renal scarring and impairment of kidney function [1]. Pyelonephritis is a common infection that primarily occurs in the outpatient setting; therefore, oral antibiotics are essential in its management [1]. Outpatients are those patients not admitted overnight to a hospital. The incidence of pyelonephritis varies depending on sex and age [1]. Estimates of outpatient pyelonephritis rates in females are 12–13 cases per 10,000 population annually [1]. International guidelines (IDSA, ESCMID) recommend outpatient management of pyelonephritis by oral ciprofloxacin, levofloxacin or oral trimethoprim-sulfamethoxazole [2]. However, there are concerns about adverse events associated with these antibiotics and increasing rates of antibiotic resistance in *Escherichia coli*, the aetiological agent accounting for approximately 90% of pyelonephritis [2–4]. Alternative oral antibiotics must be reconsidered to avoid the need for intravenous therapy, and its associated increased costs and hospitalisations. We hypothesised that antibiotics previously not included in international guidelines may be viable oral antimicrobial alternatives. The objectives of this research are to perform a systematic review of randomised controlled trials to describe the clinical efficacy and safety of oral antibiotics for the treatment of pyelonephritis in adults.

Material and methods

We conducted a systematic review to identify randomised controlled trials (RCTs) involving the treatment of acute

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pyelonephritis with oral antibiotics in non-pregnant adults. Search terms included "pyelonephritis", "antibiotic" and "treatment" (see Online Resource 1). Pyelonephritis was defined as a bacterial infection of the renal pelvis and kidney, not including prostatitis or renal abscess. Studies including intravenous therapy followed by oral therapy were excluded. Studies involving patients with complicated pyelonephritis, defined as known diabetes/metabolic disease or known structural/functional urological abnormalities were excluded. Pregnant adults were excluded as pregnancy-related anatomical changes may affect the upper urinary tract and so impact on assessments of efficacy. We did not include being male and urinary catheterisation within our definition of complicated pyelonephritis; these were considered features of a complicated lower urinary tract and so of limited relevance to clinical cure in pyelonephritis. Only adults were included, as evidence for children already supports the use of a larger range of oral antibiotic options [5]. Included studies required the presence of clinical or microbiological evaluation as an outcome measure. A search of three major databases (MEDLINE, Embase+ Embase classic and CENTRAL) and manual reference searching of relevant reviews was conducted. A search of the CDSR (Cochrane Database for Systematic Reviews) was used to identify previously published reviews that may contain relevant studies. Manual reference searching was subsequently performed, including searching current UK and international treatment guidelines [2, 6]. Grey literature was omitted due to concerns regarding the reliability of study design without peer review. Abstracts (and if required full texts) identified in the primary database search were screened independently for eligibility (authors JC, AVR). Any disagreements were referred to a third reviewer (author AK). Data collection included clinical cure, microbiological cure, adverse events (including *Clostridium difficile*) and the percentage of infections included in efficacy analyses caused by *E. coli*. These outcomes were variably defined between studies, with definitions provided in Tables 1, 2 and 3. Data were extracted directly into an electronic database within a Microsoft Word 2010 document (author JC). Proportions of those clinically or microbiologically cured were used for summary measures. Data verification was performed (author AK). A meta-analysis of data was inappropriate due to variation in interventions and methodology; therefore a descriptive approach was adopted. Quality assessment was carried out using the Cochrane Collaboration's Tool for Assessing Risk of Bias [7]. Details of the systematic review and risk of bias assessments are presented in Online Resource 1.

Results

Included studies A total of 277 studies were reviewed, and after exclusions, five studies matched all eligibility criteria and were included in the review (see Online Resource 1) [8–12]. All five studies were RCTs based in the USA or Europe conducted between 1992 and 2002. Identified studies enrolled a total of 1003 participants. Definitions of diagnosis and cure for each study are shown in Table 1. Antibiotics included were cefaclor, ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, loracarbef, norfloxacin, rufloxacin and trimethoprim-sulfamethoxazole. *E. coli* was consistently the most common infecting organism and was responsible for 56.4 to 92.5% of pyelonephritis cases (Online Resource 1).

Antibiotic treatment outcomes The most common timings for outcome assessments were 5 to 9 days post-treatment and 4 to 6 weeks after treatment. The clinical success of cefaclor, ciprofloxacin, levofloxacin, loracarbef and norfloxacin at 5 to 9 days and 4 to 6 weeks post-treatment was comparable at between 84 to 95% and 83 to 95% respectively [8–11]. The beta-lactam antibiotics achieved microbiological cure rates at 5 to 9 days and 4 to 6 weeks post-treatment of 76 and 50% for cefaclor and 81 and 64% for loracarbef respectively [11]. Ciprofloxacin and levofloxacin achieved higher rates of microbiological cure at 5 to 9 days post-treatment (85 to 94%), and at 4 to 6 weeks post-treatment microbiological cure rates were 72 to 87% [9, 10]. All clinical and microbiological outcomes are shown in Table 2.

Adverse events There were relatively high rates of adverse events identified in the Talan et al. trial of ciprofloxacin (24%) and trimethoprim-sulfamethoxazole (33%) [12]. Combining adverse event results for ciprofloxacin these were most commonly gastrointestinal-related adverse events and for trimethoprim-sulfamethoxazole, headaches presented most commonly. Other trials of ciprofloxacin reported adverse events in 8% and no adverse events [9, 10]. There were also relatively high study dropout rates in the Talan et al. trial of ciprofloxacin (11%) versus trimethoprim-sulfamethoxazole (6%) [12] (see Table 3). The Talan et al. trial was the only trial to report questioning patients to identify adverse events specifically; this may explain their higher rates of reported adverse events [12]. Levofloxacin, also recommended in international guidelines for the treatment of pyelonephritis, had a low rate at 2% of adverse events reported. All papers reported adverse events, but studies reported different adverse reactions and did not null report. *Clostridium difficile* infections were not reported.

Quality of evidence-assessing bias and heterogeneity There was significant variation between trial methodologies, including inclusion and exclusion criteria, time to follow-up, a diagnosis of pyelonephritis, a definition of cure and nomenclature used. Table 1 describes individual trial classifications. Biases were frequent and were identified for attrition, selection, performance and detection bias (see Online Resource 1). All

Table 1 Definitions of diagnosis and cure in studies included in the assessment of oral antibiotics for the treatment of pyelonephritis

Study	Number of patients enrolled, study setting and age	Inclusion criteria: considered symptoms and signs	Inclusion criteria: bacteriuria[D]	Inclusion criteria: pyuria[C]	Exclusion criteria	Microbiological cure	Clinical cure	Analysis method[B]
Cox [8]	84 Setting: unknown Age (mean): ~54 years Female 57%:	Fever (> 38 °C), back pain	$\geq 10^5$ cfu/mL	> 10 WBC/mm^3 (unspun urine) or positive leukocyte esterase or > 5 WBC/hpf (re-suspended, unstained)	Breast-feeding More than 1 dose of antibiotic within the last 3 days Prostatitis Renal insufficiency	$< 10^4$ cfu/mL	All or most signs and symptoms improved or resolved	Efficacy analysis
Richard [9]	186 Setting: unknown Age (means): 34–54 years Female: 87%	Fever (> 38 °C oral, > 39 °C rectal) flank pain, costovertebral angle tenderness	$\geq 10^5$ cfu/mL	>5 WBC/hpf or > 20 WBC/hpf	Breast-feeding Improved or stabilised on more than 24-h antibiotic therapy Permanent urinary catheterisation Previous antibiotic therapy within the last 24 h Severe illness requiring intravenous antibiotics or a second antibiotic Renal impairment	$<10^4$ cfu/mL in urine	All signs/symptoms resolved	Efficacy analysis
Bach [10]	110 Setting: outpatients Age (means): 46–53 years. Female: 59%	Fever (> 38 °C), flank pain, costovertebral angle tenderness, lower UTI symptoms	$\geq 10^5$ cfu/mL	No criteria given	Antibiotics within the last 3 days Breast-feeding Life-threatening diseases with sepsis Poor general condition Renal impairment	$< 10^2$ cfu/mL	All signs/symptoms resolved	Per protocol analysis[A]
Hyslop [11]	245 Setting: outpatients Age (means): 41–49 years Female: 81%	Fever (> 38.0 °C), flank pain	$\geq 10^5$ cfu/mL	Granulocyte casts (spun urinary sediment)	Antibiotics within the last 3 days Breast-feeding Foley catheter Renal impairment Significant co-morbidities	$< 10^4$ cfu/mL	Symptoms resolved	Efficacy analysis
Talan [12]	378 Setting: outpatient Age (medians): 23–25 years Female:100%	Fever (> 38 °C oral, > 38.6 °C rectal), flank pain, costovertebral angle tenderness	$\geq 10^4$ cfu/mL (clean catch) or $\geq 10^3$ cfu/mL (catheter)	≥ 8 leukocytes per μL (haemocytometer) or > 5 WBC/hpf^3 (sediment examination method)	Antibiotics within the last 3 days Breast feeding Hospital admission Immunocompromised Renal impairment Severe sepsis	$< 10^4$ cfu/mL (clean catch) or $< 10^3$ cfu/mL (catheter)	All signs/symptoms resolved	Efficacy analysis

[A] Intention-to-treat analysis available but not reported in this review

[B] Efficacy evaluations/per protocol were not intention-to-treat analysis. In efficacy evaluations patients were excluded from analyses after randomisation based principally on microbiological testing including not meeting bacterial growth criteria or antibiotic susceptibility criteria

[C] *wbc* white blood cell, *hpf* high power field

[D] *cfu* colony forming units

Table 2 Clinical and microbiological success of oral antibiotic regimens for the treatment of pyelonephritis

Treatment	Study	Clinical and microbiological cure, *n* (%)						
		2–3 days	4–11 days	5–9 days	14 days	22–48 days	29–42 days	4–6 weeks
Gatifloxacin 400 mg once daily 7–10 days	Cox [8]			*25/25[c] (100)* 23/25[m] (92)			*22/25[c] (88)* 18/23[m] (78)	
Ciprofloxacin 500 mg twice daily 7–10 days	Cox [8]			*19/20 [c] (95)* 17/20 [m] (85)			*18/19[c] (95)* 13/17[m] (76)	
Levofloxacin 250 mg once daily 7–10 days	Richard [9]			*82/89[c] (92)[F]* 84/89[m] (94) [F]				62/71[m] (87)
Ciprofloxacin 500 mg twice daily 10 days	Richard [9]			*51/58[c] (88)*				
Lomefloxacin 400 mg once daily 14 days	Richard [9]			*31/39[c] (80)*				
Rufloxacin 200 mg once daily[E] 14 days	Bach [10]	*21/28[c] (75)* 18/28[m] (64)			*23/27[c] (82)* 19/27[m] (70)			*24/27[c] (86)* 21/27[m] (78)
Ciprofloxacin 500 mg twice daily 10 days	Bach [10]	*26/35[c] (74)* 29/35[m] (83)			*32/34[c] (91)* 21/32[m] (66)			*31/34[c] (89)* 23/32[m] (72)
Loracarbef 400 mg twice daily 14 days minimum	Hyslop [11]			*59/68[c] (87)* 55/68[m] (81)				*48/56[c] (86)* 36/56[m] (64)
Cefaclor 500 mg three times daily 14 days minimum	Hyslop [11]			*23/25[c] (92)* 19/25[m] (76)				*10/12[c] (83)* 6/12[m] (50)
Norfloxacin 400 mg twice daily 14 days minimum	Hyslop [11]			*36/43[c] (84)* 33/43[m] (77)				*32/36[c] (89)* 30/36[m] (83)
Ciprofloxacin 500 mg twice daily 7 days	Talan [12]		*72/75[c] (96)* 75/75[m] (100)			*63/71[c] (89)* 60/72[m] (83)		
Trimethoprim-sulfamethoxazole 160/800 mg twice daily 14 days	Talan [12]		*66/78[c] (85)* 61/72[m] (85)			*58/74[c] (78)* 54/75[m] (72)		

Clinical and microbiological success for each antibiotic and administered dose is displayed in relation to the follow-up visit during which data was collected. Day of visit is displayed as number of days post-treatment. Duration of therapy is displayed as number of days including day one of treatment. Fractions indicate number of patients considered 'cured' within the treatment group, out of the total number of patients evaluated. The definition of 'cure' varies between papers. Clinical success is given in days post-treatment

[E] Plus 400 mg loading dose on day one

[F] Two treatment groups combined for outcome reporting

[m] Microbiological cure

[c] Clinical cure (in italics text)

Table 3 Adverse events reported in studies

Antibiotic	Study	Adverse events reported	Most common adverse events	Drop outs due to adverse events	Patients with adverse events
Cefaclor	Hyslop (1992)	Maculopapular rash, diarrhoea, headache, nausea, allergic reaction	Nausea	na	na
Ciprofloxacin	Cox (2002) Bach (1995) Richard (1998) Talan (2000)	Dizziness, abdominal pain, insomnia, headache, vaginitis, dyspepsia, non-identified gastrointestinal events, nausea, vomiting, diarrhoea	Nausea[a,d], gastrointestinal[c]	na[a] 0/57 (0%)[b] 0/80 (0%)[c] 21/191 (11%)[d]	na[a] 0/57 (0%)[b] 6/80 (8%)[c] 46/191 (24%)[d]
Gatifloxacin	Cox (2002)	Nausea, vomiting, diarrhoea	Nausea	na	na
Levofloxacin	Richard (1998)	Flatulence, vaginitis, diarrhoea	Flatulence, vaginitis, diarrhoea	0/124 (0%)	3/124 (2%)
Lomefloxacin	Richard (1998)	Dermatologic	Dermatologic	1/55 (2%)	3/55 (6%)
Loracarbef	Hyslop (1992)	Diarrhoea, headache, nausea	Nausea	na	na
Norfloxacin	Hyslop (1992)	Maculopapular rash, diarrhoea, nausea, allergic reaction	Nausea	na	na
Rufloxacin	Bach (1995)	Sweating, dizziness, insomnia, vomiting	Insomnia, dizziness, sweating	1/53 (2%)	4/53 (8%)
Trimethoprim-sulfamethoxazole	Talan (2000)	Rash, headache, dizziness, nausea, vomiting, diarrhoea	Headache	11/187 (6%)	62/187 (33%)

Adverse events are displayed in relation to treatment group. Adverse events were included if defined as 'possibly', 'probably' or 'definitely' related to the study drug. The numerator indicates number of patients, the denominator the total number assessed for adverse events. na, not applicable: In Hyslop et al. [10], percentages of patients affected by adverse events were not reported for all patients and so were omitted. In Cox et al. [7], it was not clear how many patients overall were assessed for adverse events

[a] Data from Cox et al.

[b] Data from Bach et al.

[c] Data from Richard et al.

[d] Data from Talan et al.

studies performed randomisation, but most studies did not describe randomisation methodology. Intention-to-treat analysis was only reported for one trial, with efficacy/per protocol analyses being the only comparable analysis [10]. Efficacy analyses consisted of post-randomisation, post-initiation of treatment reviews of clinical and microbiological features to determine participant suitability for undergoing outcome analysis. All studies included patients only if pre-treatment uropathogens were identified. All studies, except that by Talan et al., excluded patients defined by the study as having antibiotic resistance to the study antibiotics. Antibiotic resistance in identified uropathogens was therefore only reported for patients in the Talan et al. trial [8–12]. A PRISMA checklist for reporting in systematic reviews is available in Online Resource 2.

Discussion

The oral antibiotic treatment of patients with pyelonephritis is increasingly challenging. Antibiotic resistance is the primary concern, limiting antibiotic options [2]. In addition, adverse events associated with ciprofloxacin, levofloxacin and trimethoprim-sulfamethoxazole, the current oral antibiotics recommended in international guidelines, are increasingly characterised. For example, fluoroquinolones have been implicated as a principal cause of *C .difficile* infection, and trimethoprim-sulfamethoxazole use is associated with rare but severe side effects, e.g. agranulocytosis [13, 14]. On this background, it is essential to evaluate the evidence for the oral antibiotic treatment of pyelonephritis, in particular, if there are options available when resistance to recommended antibiotics occurs and to reduce adverse events associated with antibiotic consumption. Our analysis suggests norfloxacin may be appropriate for the outpatient management of pyelonephritis, with comparable clinical cure rates to ciprofloxacin and levofloxacin. Norfloxacin is less active against anaerobes, Streptococci and Enterobacteriaceae than ciprofloxacin and levofloxacin [15]. As these bacteria form a significant component of the colonic microbiome, it is biologically plausible that norfloxacin will disrupt the colonic microbiome to a lesser degree than ciprofloxacin and levofloxacin. Given the large numbers of patients treated with the fluoroquinolones, including ciprofloxacin and levofloxacin, an antibiotic with less impact on the microbiome, such as norfloxacin may be necessary for reducing the spread of antibiotic-resistant bacteria at the national level. Indeed, various national guidelines advocate choosing antibiotics with the most narrow spectrum available [16]. For individual patients, using norfloxacin may also offer potentially important benefits when considering the high rates of adverse events associated with ciprofloxacin and trimethoprim-sulfamethoxazole consumption. In addition, our review suggests oral beta-lactam antibiotics may be appropriate for the outpatient treatment of pyelonephritis, which contrasts with international guidelines that suggest that oral beta-lactams as a group are less effective than fluoroquinolones and trimethoprim-sulfamethoxazole [4]. This review identifies data, which suggests oral cefaclor and loracarbef have clinical cure rates comparable to ciprofloxacin and levofloxacin at 5 to 9 days and 4 to 6 weeks post-therapy reviews. Whilst loracarbef (a carbacepham beta-lactam antibiotic) and other quinolone antibiotics identified in this review (gatifloxacin, lomefloxacin and rufloxacin) may not be commercially available, their inclusion in the review is justified as they support assessments of antibiotic class efficacy. Again, for patients where quinolones and trimethoprim-sulfamethoxazole are not appropriate, via allergy, intolerance or bacterial resistance, availability of an alternative class of antibiotic may be beneficial. For example, it may prevent the need for community-based patients to be hospitalised for intravenous antibiotics. Our findings differ from other reviews of literature in this area, as we allowed trials with male patients and patients with urinary catheters to be included; other reviews excluded such studies classing them as complicated pyelonephritis [4]. Additionally, we formally assess adverse event rates.

Microbiological outcomes were reported in all trials, with microbiological efficacies generally lower than clinical efficacies. The clinical relevance of microbiological outcomes is becoming increasingly unclear with an evolving evidence base supporting a potentially protective role of asymptomatic bacteriuria against clinical infection [17].

In this review, the highest rates of adverse events and study dropouts were reported from one trial of ciprofloxacin and trimethoprim-sulfamethoxazole [12]. Therefore, the efficacy of these antibiotics and the recommendations for their use need to be balanced against the possibility of higher adverse event rates. Our analysis identified significant inter-study variation in adverse events rates for the same antibiotic, which is likely to be reflective of the heterogeneity in assessment and reporting of adverse events, and caution should be used in comparing reported adverse event rates.

The findings that oral norfloxacin and beta-lactam antibiotics may be effective in the treatment of patients with pyelonephritis needs considering in the context of bias and heterogeneity within included studies. The studies are heterogeneous in their inclusion and exclusion criteria, definitions of cure and timings of post-treatment assessments, and we acknowledge the limitations this brings to the review. Differences in the age of study participants may also have had an impact on outcomes. The individual studies also have varying risks of bias, which will have an impact on results. For example, only one study was designed with intention-to-treat analysis. Although this increases the risk of bias, this does allow consideration to be given to the efficacy of treatments in specific populations given their resistance rates, and

individuals with known susceptibility data. Efficacy analyses are also of benefit when considering the age of the studies, as intention-to-treat analysis from 1992 to 2002 may be less relevant in an era of increased antibiotic resistance. The identified study limitations highlight the need for a core outcome set of data to be collected in future trials, including both cure rates and adverse events, for studies of patients with pyelonephritis. Standardised diagnostic criteria and outcome measures would ensure directly comparable results. This would allow for future meta-analyses and an improvement of the external validity of the conclusions made. It has been over 15 years since an RCT trial of oral antibiotics for pyelonephritis was carried out, also supporting the need for future trials. In summary, our review has identified clinical data in support of oral norfloxacin and cefaclor for the outpatient treatment of pyelonephritis. Further, high-quality RCTs are required to investigate the role of these antibiotics in the oral antibiotic management of pyelonephritis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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