Pyelonephritis (acute) in non-pregnant women

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Ignacio Neumann, M Fernanda Rojas, and Philippa Moore

ABSTRACT

INTRODUCTION: Pyelonephritis is usually caused by ascent of bacteria, most often Escherichia coli, from the bladder, and is more likely in people with structural or functional urinary tract abnormalities. The prognosis is good if pyelonephritis is treated appropriately, but complications include renal abscess, renal impairment, and septic shock. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of: oral antibiotic treatments for acute pyelonephritis in women with uncomplicated infection; antibiotic treatments in women admitted to hospital with complicated infection; inpatient versus outpatient management in women with uncomplicated infection; analgesia in uncomplicated acute pyelonephritis? We searched: Medline, Embase, The Cochrane Library and other important databases up to February 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 5 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: analgesics, inpatient management, intravenous antibiotics, non-opioids, non-steroidal anti-inflammatory drugs, oral antibiotics, outpatient management, urinary analgesics.

QUESTIONS

INTERVENTIONS

Footnote

*Categorisation is not based on placebo-controlled RCTs. Such studies are likely to be considered unethical.

Key points

- Pyelonephritis is usually caused by ascent of bacteria from the bladder, most often *Escherichia coli*, and is more likely in people with structural or functional urinary tract abnormalities.

The prognosis is good if pyelonephritis is treated appropriately, but complications include renal abscess, renal impairment, and septic shock.

- Consensus is that oral antibiotics, given in the outpatient setting, are effective in non-pregnant women with uncomplicated pyelonephritis, although no placebo-controlled studies have been found.

  We don't know whether any one treatment regimen is more effective, or what the optimum duration of treatment is, although it may be sensible to continue treatment for at least 10 days.

  Broader spectrum antibiotics, such as quinolones, may be more effective compared with narrower spectrum antibiotics, such as ampicillin, amoxicillin, or co-trimoxazole, in areas where resistance to these is common.

  In the outpatient setting, we don't know whether intravenous antibiotics are more effective in non-pregnant women with uncomplicated pyelonephritis compared with oral regimens.

- Intravenous antibiotics are considered effective in women admitted to hospital with uncomplicated pyelonephritis.

  We don't know which is the most effective intravenous antibiotic regimen, or the optimum duration of treatment.

  Combining intravenous plus oral antibiotics may be no more effective that oral antibiotics alone, but the evidence is weak.

- We don't know whether inpatient treatment improves outcomes compared with outpatient treatment.

- We found no evidence that simple analgesics ,NSAIDs, or urinary analgesics reduce pain from uncomplicated pyelonephritis.

  NSAIDs may worsen renal function and should be used in caution in women with pyelonephritis.

DEFINITION

Acute pyelonephritis, or upper urinary tract infection, is an infection of the kidney characterised by pain when passing urine, fever, chills, flank pain, nausea, and vomiting. White blood cells are almost always present in the urine. White blood cell casts are occasionally seen on urine microscopy. There is no consensus on the definitions for grades of severity. However, in practice, people with acute pyelonephritis may be divided into people who are able to take oral antibiotics, who do not have signs of sepsis, and may be managed at home, and those who require intravenous antibiotics in hospital. Some consider the absolute indications for hospitalisation to be persistent vomiting, progression of uncomplicated urinary tract infection, suspected sepsis, or urinary tract obstruction. [1] Pyelonephritis is considered uncomplicated if caused by a typical pathogen in an immunocompetent person who has normal renal anatomy and renal function. [2] There is little difference in the treatment of men and non-pregnant women. **Diagnosis:** Women presenting with fever and back pain suggest a possible diagnosis of acute pyelonephritis. [3] Urinalysis and urine culture should be performed to confirm the diagnosis. Pyuria is present in almost all patients and can be detected rapidly with leukocyte esterase test (S: 74% to 95% and E: 94% to 98%) or the nitrite test (S: 92% to 100% and E: 35% to 85%). [1] Bacterial growth of 104-10-5 is 10.000-100.000 colony forming units on urine culture of a mid-stream specimen will confirm bacteriological diagnosis. [4]

INCIDENCE/ PREVALENCE

The estimated annual incidence per 10,000 people is 27.6 cases in the USA [5] and 35.7 cases in South Korea. [6] Worldwide prevalence and incidence are unknown. The highest incidence of pyelonephritis occurs during the summer months. [3] Women are approximately five times more likely than men to be hospitalised with acute pyelonephritin. [1]

AETIOLOGY/ RISK FACTORS

Pyelonephritis is most commonly caused when bacteria in the bladder ascend the ureters and invade the kidneys. In some cases, this may result in bacteria entering and multiplying in the bloodstream. The most frequently isolated organism is *Escherichia coli* (56–85%); others include *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. [5] [7] [8] In eldery people, *E.coli* is less common (60%), whereas people who have diabetes mellitus tend to have infections caused by Klebsiella, Enterobacter, Clostridium, or Candida. [1] People with structural or functional urinary tract abnormalities are more prone to pyelonephritis that is refractory to oral therapy or complicated by bacteraemia. Risk factors associated with pyelonephritis in healthy women are sexual intercourse, use of spermicide, urinary tract infection in the previous 12 months, a mother with a history of urinary tract infection, diabetes, and urinary incontinence. [5] The most important risk factor for complicated urinary tract infection is obstruction of the urinary tract. [9] The incidence of drug-resistant microorganisms varies in different geographical areas. Recent hospitalisation, recent use of antibiotics, immunosuppression, recurrent pyelonephritis, and nephrolithiasis increase the risk of drug resistance. [7]

PROGNOSIS

Prognosis is good if uncomplicated pyelonephritis is treated appropriately. Complications include renal abscess, septic shock, and renal impairment, including acute renal failure. Short-term independent risk factors for mortality include age above 65 years, septic shock, being bedridden, and immunosuppression. [7] Conditions such as underlying renal disease, diabetes mellitus, and im-

munosuppression may worsen prognosis, but we found no good long-term evidence about rates of sepsis or death among people with such conditions.

AIMS OF INTERVENTION To reduce the duration and severity of symptoms; to prevent or minimise potential complications, with minimum adverse effects.

OUTCOMES Urine culture after treatment; signs and symptoms; rates of complications of infection; and adverse effects of treatment.

METHODS *BMJ Clinical Evidence* search and appraisal February 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2007, Embase 1980 to February 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). We also searched for retractions of studies included in the Review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We excluded studies that were primarily in men, pregnant women, and people with complicated pyelonephritis, or prone to pyelonephritis because of indwelling catheters, or anatomical or functional bladder abnormalities. Most studies examined both men and women, and we have stated how many women were included, when available. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14).

QUESTION What are the effects of oral antibiotic treatments for acute pyelonephritis in women with uncomplicated infection?

OPTION ANTIBIOTICS (ORAL) VERSUS PLACEBO*

We found no direct information about whether oral antibiotics are better than no active treatment. However, consensus holds that these drugs are effective.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, see table, p 14 .

Benefits: We found no systematic review or RCTs (see comment below).

Harms: We found no RCTs.

Comment: The lack of placebo-controlled RCTs may reflect that experimental trials would be considered unethical. However, consensus holds that these drugs are effective.

OPTION ANTIBIOTICS (ORAL) VERSUS EACH OTHER

Cure rates

Oral antibiotics compared with each other There seems to be no significant difference between different oral antibiotics in increasing cure rates of uncomplicated acute pyelonephritis (very low-quality evidence).

Note

We found no direct information comparing different lengths of treatment with the same oral antibiotic.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, see table, p 14 .

Benefits: We found two systematic reviews which contained RCTs comparing different oral antibiotics in acute pyelonephritis (see table 1, p 10 and table 2, p 11). [10] [4] Both reviews included RCTs on ambulatory patients and patients in hospital. Most excluded people with complicating factors such as structural abnormalities of the urinary tract, additional diseases, pregnancy, or signs of possible sepsis. The first systematic review (search date 1991, 9 RCTs comparing oral antibiotics, 470 men

and non-pregnant women; see comment below;) found five RCTs conducted in outpatients and four in inpatients. [10] The studies were conducted in the USA, Europe, and Peru. All RCTs included in the review included more women than men. All but one of the RCTs in the review found no significant difference between different antibiotics in rates of early cure (negative urine culture within 7–10 days), and six of the RCTs found no significant difference in rates of late cure (negative urine culture 2–4 weeks or more after stopping treatment). However, several of the included RCTs were too small to detect a clinically important difference between antibiotic regimens. The second systematic review did not include a meta-analysis (search date 2004, 29 RCTs in children and adults, none of which was included in the first systematic review, 9 RCTs were in adults, and compared oral antibiotics). [4] No data were available about the country of origin of the RCTs included, nor of the proportion of male or female participants in the RCTs; but, given the higher prevalence of pyelonephritis in women, we assumed that the RCTs included more women than men. As no meta-analysis was performed it is difficult to draw conclusions. However, there appears to be no difference between the oral antibiotics (less than 10% difference between clinical success and failure rates).

Duration of treatment:
We found no RCTs comparing the same oral antibiotic given for two different time periods. Most of the studies identified above gave antibiotic therapy for 10 days or longer.

Harms: Neither of the systematic reviews reported adverse effects of treatment. [10] [4] One RCT included in the second systematic review enrolled all participants who had taken at least one dose of the trial drug in a safety analysis, regardless of whether they had taken part in the final evaluation. [11] It reported adverse effects in 3/124 [2%] people taking levofloxacin, 6/80 [8%] people taking ciprofloxacin, and 3/55 [5%] people taking lomefloxacin. Gastrointestinal symptoms were common with both ciprofloxacin and levofloxacin, whereas rash was the most common adverse effect with lomefloxacin. One of the 186 people discontinued treatment (lomefloxacin) because of adverse effects. Another RCT included in the second systematic review found that gatifloxacin 400 mg increased the incidence of adverse events and withdrawal compared with gatifloxacin 200 mg and ciprofloxacin (adverse events: 64/366 [17%] with ciprofloxacin *v* 78/374 [21%] with gatifloxacin 200 mg *v* 143/382 [37%] with gatifloxacin 400 mg; withdrawal: 7/366 [1.9%] with ciprofloxacin *v* 7/374 [1.9%] with gatifloxacin 200 mg *v* 15/382 [3.9%] with gatifloxacin 400 mg; significance not reported).

Duration of treatment:
We found no RCTs (see Clinical guide under comments below).

Comment: **Clinical guide:** We found no evidence from RCTs to support the use of any particular antibiotic over the others tested. Local resistance rates should always be considered when deciding which antibiotic to use. Broader spectrum antibiotics, such as quinolones, may be more effective compared with narrower spectrum antibiotics, such as ampicillin, amoxicillin, or co-trimoxazole, in areas where resistance to these is common. The second most-studued antibiotic in RCTs after co-trimoxazole is ciprofloxacin, and may be a good first choice. Given the lack of good evidence regarding duration of treatment, it should probably not be given for less than 10 days.

OPTION ORAL VERSUS INTRAVENOUS ANTIBIOTICS

We found no clinically important results about oral antibiotics compared with intravenous antibiotics in women with uncomplicated pyelonephritis.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits: We found no systematic review or RCTs comparing oral versus intravenous antibiotics in women with uncomplicated pyelonephritis.

Harms: We found no RCTs.

Comment: See comment on Oral antibiotics versus placebo.

QUESTION What are the effects of antibiotic treatments for acute pyelonephritis in women admitted to hospital with uncomplicated infection?

OPTION ANTIBIOTICS (INTRAVENOUS) VERSUS PLACEBO

We found no direct information about whether intravenous antibiotics are better than no active treatment in women with uncomplicated pyelonephritis. Consensus holds that intravenous antibiotics are effective.

Pyelonephritis (acute) in non-pregnant women

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits: We found no systematic review or RCTs (see comment below).

Harms: We found no RCTs.

Comment: RCTs comparing antibiotics versus placebo would be considered unethical in women with uncomplicated pyelonephritis; however, consensus holds that intravenous antibiotics are effective.

OPTION ANTIBIOTICS (INTRAVENOUS) VERSUS EACH OTHER

Cure rates

Intravenous antibiotics compared with each other There seems to be no significant difference between different intravenous antibiotics in increasing cure rates of pyelonephritis (very low-quality evidence).

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits: We found one systematic review (search date 2004, 3 RCTs in adults with pyelonephritis) comparing intravenous antibiotics versus each other. [4] The systematic review did not perform either a meta-analysis or a statistical analysis, making it difficult to draw conclusions. No data were available about the country of origin of the RCTs, nor of the proportion of male or female participants, but given the higher prevalence of pyelonephritis in women, we assumed that the RCTs included more women than men. The first RCT, which did not report clinical success rate, showed a difference of 15% in bacteriological success rate (85% with co-amoxiclav *v* 100% with amoxicilin and gentamicin). The second RCT, which compared multiple doses of intravenous gentamicin with a single dose, found a higher clinical success rate with multiple doses (96% with multiple doses *v* 81% with single dose). The third RCT found similar microbiological cure rates between intravenous ispamicin and intravenous amikacin (see table 3, p 11).

Harms: The systematic review did not report adverse effects. [4]

Comment: There is consensus that the choice of empirical antibiotics when antibiotic sensitivities are not known should take into account the setting, medical history of the patient, Gram stain of the urine, previous infecting organism, and local antibiotic sensitivities.

Clinical guide:
We found no evidence from RCTs to support the use of any antibiotic in particular. Therefore, local resistance rates should always be considered when deciding which antibiotic to use. Given the lack of good evidence on treatment duration, the treatment should probably not be given for less than 10 days.

OPTION INTRAVENOUS VERSUS ORAL ANTIBIOTICS

We found no clinically important results about intravenous antibiotics compared with oral antibiotics in pyelonephritis (acute) in non-pregnant women.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits: We found no systematic review or RCTs comparing intravenous versus oral antibiotics in women with uncomplicated pyelonephritis.

Harms: We found no RCTs.

Comment: None.

OPTION INTRAVENOUS ANTIBIOTICS PLUS ORAL ANTIBIOTICS

Cure rates

Compared with oral antibiotics alone Intravenous antibiotics plus oral antibiotics are no more effective in reducing pain or fever at 48 hours compared with oral antibiotics alone (moderate-quality evidence).

Intravenous antibiotics followed by oral antibiotics compared with oral antibiotics alone Sequential treatment with an intravenous antibiotic followed by an oral antibiotic may no more effective at increasing cure rates compared with oral antibiotics alone (low-quality evidence).

Different durations of antibiotics Three days of intravenous fleroxacin plus 11 days of oral fleroxacin may be no more effective in increasing cure rates at 4–6 weeks compared with 3 days of intravenous fleroxacin plus 4 days of oral fleroxacin (very low-quality evidence).

For grade evaluation of intervention for pyelonephritis (acute) in non-pregnant women, see table, p 14 .

Benefits:

Combined treatment with intravenous plus oral antibiotics versus oral antibiotics alone:
We found one systematic review [4] which did not perform a meta-analysis (search date 2004). It identified one RCT comparing intravenous plus oral antibiotics versus oral antibiotics alone. [12] We also found one additional RCT. [13] The RCT (118 women admitted with acute uncomplicated pyelonephritis) identified by the review compared a single dose of intravenous tobramycin (2 mg/kg) plus oral ciprofloxacin (500 mg twice-daily for 10 days) versus oral ciprofloxacin plus intravenous placebo (0.9% saline solution). [12] Clinical success or failure was assessed, with failure defined as the persistence of fever or pain after 48 hours of treatment, and success as the absence of fever or pain. The RCT found no significant difference between groups in rates of clinical success (58/60 [97%] with intravenous tobramycin plus oral ciprofloxacin *v* 54/58 [93%] with oral ciprofloxacin plus placebo; RR 1.04, 95% CI 0.95 to 1.13). The additional RCT (85 women) compared ampicillin (1 g every 6 hours) versus co-trimoxazole (160 mg/800 mg twice-daily). [13] Both regimens were combined with intravenous gentamicin and followed by oral treatment with either ampicillin or co-trimoxazole. Clinical success rate was 100% in both groups. There was no significant difference in bacteriological success rates between ([90%] with v co-trimoxazol/gentamicin [92.5%]; RR 0.70, 95% CI 0.07 to 6.94).

Sequential treatment with intravenous antibiotics followed by oral antibiotics (different combinations versus each other):
We found one systematic review (search date 2004), which did not perform a meta-analysis. [4] It identified three RCTs, which found similar cure rates between different combinations of intravenous followed by oral antibiotics (see table 4), p 12 .

Sequential treatment with intravenous antibiotics followed by oral antibiotics versus oral antibiotics alone:
We found one systematic review (search date 2004), which did not perform a meta-analysis. [4] It identified three RCTs, which found similar (high) cure rates between intravenous followed by oral antibiotics and oral antibiotics alone (see table 4), p 12 .

Duration of sequential treatment:
We found one systematic review (search date 2004), which did not perform a meta-analysis. [4] It identified one RCT (54 people [36 women, 18 men]) comparing oral fleroxacin for 4 days versus oral fleroxacin for 11 days in people who had previously received intravenous fleroxacin for 3 days. [14] At 4–6 weeks follow up, it found no significant difference between groups in clinical and bacteriological success rates (clinical success rate 11/18 [61%] with 4 days' treatment *v* 11/16 [69%] with 11 days' treatment; bacteriological success rate 14/18 [78%] with 4 days' treatment *v* 12/16 [75%] with 11 days' treatment, reported as non-significant, P value not reported).

Harms:

Combined treatment with intravenous plus oral antibiotics versus oral antibiotics alone:
The review gave no information on adverse effects. [4] The RCT reported that “no undesirable side effects were observed”. [12] No further details were reported. The additional RCT found that mild adverse effects (with ampicillin: rash, diarrhoea, and vaginitis, and with co-trimoxazole: nausea, vomiting, and vaginitis) were common but no significant difference was found between groups (10/32 [32%] with ampicillin *v* 13/39 [33%] with co-trimoxazole; RR 0.90, 95% CI 0.48 to 1.85). [13]
Sequential treatment with intravenous antibiotics followed by oral antibiotics:
The review gave no information on adverse effects. [4]

Duration of sequential treatment:
The RCT found that more people in the 4-days treatment group had minor adverse effects compared with the 11-days treatment group (adverse effects experienced by 6/24 [25%] people with 4-days treatment *v* 8/21 [38%] with 11 days' treatment; P less than 0.05). [4] However, the authors of the trial noted that most adverse effects occured during the first week of treatment.

Comment:

None.

QUESTION **What is the effect of inpatient versus outpatient management for acute pyelonephritis in women with uncomplicated infection?**

OPTION INPATIENT VERSUS OUTPATIENT MANAGEMENT

We found no clinically important results about inpatient management compared with outpatient management of women with acute uncomplicated pyelonephritis.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits: We found no systematic review and no RCTs.

Harms: We found no RCTs.

Comment: Hospitals might provide closer monitoring and supervision of people with pyelonephritis than can be provided outside of hospital. However, we found no RCTs to clarify whether treatment in hospital delivers any benefit in terms of outcomes, or whether there is an increased risk of harm from hospital treatment. As clinical judgement of the severity of infection is used to determine admission to hospital, it may be difficult and perhaps unethical to perform an RCT in which patients are randomised either to hospital or ambulatory care.

QUESTION **What are the effects of analgesia in women with uncomplicated acute pyelonephritis?**

OPTION NSAIDS

We found no direct information about whether NSAIDs are better than no active treatment or simple systemic analgesics (non-opiates) in the management of women with acute uncomplicated pyelonephritis.

Adverse effects
NSAIDs are associated with impairment of renal function, and should be used with caution in uncomplicated acute pyelonephritis.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits:

NSAIDs versus placebo:
We found no systematic review or RCTs.

NSAIDs versus simple systemic analgesics (non-opiates):
We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment:

Clinical Guide:
Although we found no RCTs, NSAIDs can have nephrotoxic effects in some circumstances, suggesting that they should be used with caution in uncomplicated acute pyelonephritis.

OPTION SIMPLE SYSTEMIC ANALGESICS (NON-OPIOIDS)

We found no direct information about whether simple analgesics (excluding urinary tract analgesics and opiates) are better than no active treatment or NSAIDs in the management of women with acute uncomplicated pyelonephritis.

For grade evaluations of intervention for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits:

Simple systemic analgesics (non-opiates) versus placebo:
We found no systematic review or RCTs.

Simple systemic analgesics (non-opiates) versus NSAIDs:
We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION **URINARY ANALGESICS** New

We found no direct information about the efficacy of urinary analgesics for the treatment of acute uncomplicated pyelonephritis.

For grade evaluation of interventions for pyelonephritis (acute) in non-pregnant women, **see table, p 14 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: Despite the widespread use in some countries of smooth muscle relaxants, such as flavoxate, pargeverine, or phenazopyridine (an azo dye that exerts an analegic effect to the urinary mucosa), we found no RCTs to confirm or refute the effectiveness of these compounds.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Urinary analgesics.

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Ignacio Neumann
Pontificia Universidad Católica de Chile
Chile

M Fernanda Rojas
Pontificia Universidad Católica de Chile
Chile

Philippa Moore
Pontificia Universidad Católica de Chile
Chile

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TABLE 1 **Oral antibiotics versus each other for acute pyelonephritis: results of RCTs (see text, p ?).** [8]

First antibiotic	Total number of people	Early cure* rates %	Late cure* rates %	Comparator antibiotic	Early Cures/ Total (%)	Late Cures/ Total (%)	P value
Amoxicillin 500 mg three times daily for 14 days	28	NA	94	Co-trimoxazole 160 mg/800 mg twice daily for 14 days	NA	92	NS
Norfloxacin 400 mg twice daily for 10 days	24	100	86	Co-trimoxazole 160 mg/800 mg twice daily for 10 days	100	90	NS
Ampicillin 500 mg four times daily for 10 days	14	88	NA	Cefaclor, 250 mg, twice daily for 10 days	67	NA	NS
Norfloxacin 400 mg twice daily for 7 days or longer	15	67	NA	Co-trimoxazole 160 mg/800 mg twice daily for 7 days or longer	92	NA	NS
Co-amoxiclav 250 mg/125 mg three times daily for 10 days	104	94	85	Co-trimoxazole 160 mg/800 mg twice daily for 10 days	82	64	P = 0.02 for late cure; NS for early cure
Ampicillin 500 mg four times daily for 2 or 6 weeks	39	100	47	Co-trimoxazole 160 mg/800 mg twice daily for 2 or 6 weeks	100	91	P = 0.004 for late cure; NS for early cure
Amoxicillin 2000 mg one time dose then 1000 mg twice daily for 9 days	45	100	100	Amoxicillin 750 mg, twice daily for 12 days	96	87	NS
Cefetamet 2000 mg once daily or 1000 mg twice daily for 10–15 days	50	93	79	Cefadroxil 1000 mg, three times daily for 10-15 days	73	52	NS
Norfloxacin 400 mg twice daily for 14 days	151	91	82	Cefadroxil 1000 mg, twice daily for 14 days	59	44	P less than 0.0001 for both early and late cures

*Early cure: negative urine culture within 7–10 days of starting treatment; late cure: negative urine culture 2–4 weeks or more after stopping treatment. NA, not available; NS, not significant; TMP, Trimethoprim. Pinson AG, Philbrick JT, Lindbeck GH, et al. Oral antibiotic therapy for acute pyelonephritis; a methodologic review of the literature. *J Gen Intern Med* 1992;7:544–553. Reprinted by permission of Blackwell Science, Inc.

TABLE 2 **Oral antibiotics versus each other for acute pyelonephritis: results of RCTs (see text, p ?)** [4]

First antibiotic	Total number of people	Early cure* rates %	Late cure* rates %	Comparator antibiotic	Early Cures/ Total (%)	Late Cures/ Total (%)
Piperacillin 2 g plus tazobactam 0.5 g three times daily for 5–14 days	40	NA	58	Imipenem 0.5 g plus cilastatin 0.5 g three times daily for 5–14 days	NA	49
Isepamicin 8-15 mg daily for 4–14 days	60	NA	91	Amikacin 7.5 mg/kg twice daily for 4–14 days	NA	93
Co-amoxiclav 2.2 g three times daily (duration not specified)	48	85	NA	Gentamicin 1.5 mg/kg as single dose plus amoxicillin 2.2 g three times daily for 7–14 days	100	NA

*Early cure: negative urine culture within 7–10 days of starting treatment; late cure: negative urine culture 2–4 weeks or more after stopping treatment. NA, not available; P values not available. Piccoli GB, Consiglio V, Colla L, Mesiano P, Magnano A, Burdese M, Marcuccio C, Mezza E, Veglio V, Piccoli G. Antibiotic treatment for acute 'uncomplicated' or 'primary' pyelonephritis: a systematic, 'semantic revision'. *Int J Antimicrob Agents*. 2006;28S S49–S63

TABLE 3 **Intravenous antibiotics versus each other for acute pyelonephritis: results of RCTs (see text, p ?)** [4]

First antibiotic	Total number of people	Early cure* rates %	Late cure* rates %	Comparator antibiotic	Early Cures/ Total (%)	Late Cures/ Total (%)
Piperacillin 2 g plus Tazobactam 0.5 g three times daily for 5–14 days	40	NA	58	Imipenem 0.5 g plus cilastatin 0.5 g three times daily for 5–14 days	NA	49
Isepamicin 8–15 mg daily for 4–14 days	60	NA	91	Amikacin 7.5 mg/kg twice daily for 4–14 days	NA	93
Co-amoxiclav 2.2 g three times daily (duration not specified)	48	85	NA	Gentamicin 1.5 mg/kg as single dose plus amoxicillin 2.2 g three times daily for 7–14 days	100	NA

*Early cure: negative urine culture within 7–10 days of starting treatment; late cure: negative urine culture 2–4 weeks or more after stopping treatment. NA, not available; P values not available. Piccoli GB, Consiglio V, Colla L, Mesiano P, Magnano A, Burdese M, Marcuccio C, Mezza E, Veglio V, Piccoli G. Antibiotic treatment for acute 'uncomplicated' or 'primary' pyelonephritis: a systematic, 'semantic revision'. *Int J Antimicrob Agents*. 2006;28S S49–S63

TABLE 4 **Intravenous plus oral antibiotics combinations versus each other or versus oral antibiotics alone for acute pyelonephritis: results of RCTs (see text, p ?) [4]**

First antibiotic combination	Total number of people	Early cure* rates %	Late cure* rates %	Comparator antibiotic combination	Early Cures/ Total (%)	Late Cures/ Total (%)
Intravenous plus oral antibiotics combinations versus each other						
Ertapenem iv 1 g daily for 3 days then ciprofloxacin orally 500 mg twice daily for 10–14 days	80	NA	86.5	Ceftriaxone iv 1 g daily for 3 days then ciprofloxacin orally 500 mg twice daily for 10–14 days	NA	89
Ceftriaxone iv 1 g daily until urine culture results then oral treatment based on sensitivity analysis for 10 days	105	100	NA	Ceftriaxone iv 1 g single dose then cefixime orally 400 mg daily then oral treatment based on sensitivity analysis for 10 days	100	NA
Ertapenem iv 1 g daily for 4–6 days then ciprofloxacin orally 500 mg twice daily for 7–10 days	153	NA	95	Ceftriaxone iv 1 g daily for at least 3 days then ciprofloxacin orally 500 mg twice daily for 7–10 days	NA	95
Cefuroxime iv 0.75-1.5 g daily for 2–4 days then ceftibuten orally 200 mg twice daily for 10 days	158	NA	75	Cefuroxime iv 0.75–1.5 g daily for 2–4 days then norfloxacin orally 400 mg twice daily for 10 days	NA	89
Cefotaxime iv 1 g twice daily for 2 days then Cefadroxil orally 1 g twice daily for 10 days	73	NA	63	Cefotaxime iv 1 g twice daily for 2 days then tobramycin orally 160 mg daily for 2 days then Cefadroxil 1 g daily for 10 days	NA	59
Fleroxacin iv 400 mg daily for 3 days then Fleroxacin orally 400 mg daily for 7 days	54	NA	61	Fleroxacin iv 400 mg daily for 3 days then Fleroxacin orally 400 mg daily for 14 days	NA	69
Gentamicin iv 10 mg/kg single dose then Ciprofloxacin orally 250 mg twice daily for 5 day	41	93	NA	Gentamicin iv 2.5 mg/kg single dose, then according to blood levels and when clinical improvement switch to Ciprofloxacin orally 250 mg twice daily for 5 day	92	NA
Ampicillin iv 600 mg or mecillinam iv 300 mg twice daily until 30 hours after defervescence then Pivampicillin orally 500 mg or Pivmecillinam 400 mg twice daily for 4–14 days	136	NA	63	Cefotaxim iv 1 g until 30 hours after defervescence then Cefadroxil orally 800 mg twice daily for 4–14 days	NA	6
Intravenous plus oral antibiotics versus antibiotics alone						

First antibiotic combination	Total number of people	Early cure* rates %	Late cure* rates %	Comparator antibiotic combination	Early Cures/ Total (%)	Late Cures/ Total (%)
Tobramycin iv 2 mg/kg single dose then ciprofloxacin orally 500 mg twice daily for 10 days	118	NA	100	Placebo iv single dose then ciprofloxacin orally 500 mg twice daily for 10 days	NA	98
Ciprofloxacin iv 200 mg twice daily for 3 days then ciprofloxacin orally 500 mg twice daily (duration not specified)	141	97	NA	Ciprofloxacin orally 500 mg twice daily (duration not specified)	98	NA
Netilmicin iv 4 mg/kg daily for 5 days then amoxicillin orally 1 g three times daily for 12 days then oral treatment according to the antibiogram for 12 days	126	NA	100	Cefixime orally 200 mg twice daily for 12 days	NA	100

*Early cure: negative urine culture within 7–10 days of starting treatment; late cure: negative urine culture 2–4 weeks or more after stopping treatment. NA, not available; P values not available. Piccoli GB, Consiglio V, Colla L, Mesiano P, Magnano A, Burdese M, Marcuccio C, Mezza E, Veglio V, Piccoli G. Antibiotic treatment for acute 'uncomplicated' or 'primary' pyelonephritis: a systematic, 'semantic revision'. *Int J Antimicrob Agents*. 2006;28S S49–S63

TABLE **GRADE evaluation of interventions for pyelonephritis (acute) in non-pregnant women**

Important outcomes	**Cure rates, treatment failure, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of oral antibiotic treatments for acute pyelonephritis in women with uncomplicated infection?									
12 (618) [10]	Cure rates	Oral antibiotics *v* each other	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for inclusion of men and children
What are the effects of antibiotic treatments for acute pyelonephritis in women admitted to hospital with uncomplicated infection?									
3 (148) [15]	Cure rates	Intravenous antibiotics *v* each other	4	–3	–1	–2	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and insufficient evidence to enable comparisons to be made. Consistency point deducted for different results for different regimens. Directness point deducted for inclusion of small number of different comparators and uncertainty of inclusion of male participants
2 (203) [12] [13]	Treatment success	Intravenous plus oral *v* oral antibiotics	4	0	0	–1	0	Moderate	Directness point deducted for small number of comparisons
3 (385) [15]	Cure rates	Sequential treatment (iv *v* oral)	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of different comparator in one study
1 (54) [14]	Cure rates	Duration of sequential treatment) 11 days *v* 4 days of antibiotics	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of male participants

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.