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Guideline

AAUS guideline for acute uncomplicated pyelonephritis

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A B S T R A C T

Patients with acute uncomplicated pyelonephritis often show impaired immune function that aggravates infectious diseases. Some of the therapeutic recommendations for UTIs have been revised recently, partly because of the emergence of antibiotic resistant bacteria such as quinolone-resistant *Escherichia coli* and Extended spectrum beta-lactamase (ESBL) producing bacteria, mainly *E. coli* and *Klebsiella pneumoniae*, which vary from country to country or between regions in frequency of emergence and spread. An era of antimicrobial resistance (AMR) has arrived, where the use of antibiotics should be reconsidered.

Several newly established antimicrobial agents are commercially available for the treatment of resistant bacteria, such as penicillins or cephalosporins with beta-lactamase inhibitors. This new edition of Asian Association of UTI & STI (AAUS) guideline for acute uncomplicated pyelonephritis includes new recommendations for antibiotic use based on changing trends in antibiotic resistance.

1. Introduction

Acute uncomplicated pyelonephritis remains one of the most common indications for prescribing of antimicrobials to otherwise healthy community-dwelling women. Despite published guidelines for the optimal selection of an antimicrobial agent and duration of therapy, studies demonstrate wide variations in prescribing practices [1–5] (see Tables 1 and 2).

The focus of this guideline is the treatment of women with acute uncomplicated pyelonephritis, with diagnoses limited in these guidelines to premenopausal, non-pregnant women with no known urological abnormalities or comorbidities. It should be noted that women who are postmenopausal or have well-controlled diabetes without urological sequelae may be considered by some experts to have uncomplicated UTI, but a discussion of specific management of these groups is outside the scope of this guideline.

The issues of *in vitro* resistance prevalence and the potential for collateral damage were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

Basically, the present state of antimicrobial resistance development is alarming [6]. Antibiotic resistance in Asian countries mirrors the global increase in resistant strains [7,8], especially the steadily increasing occurrence of ESBL producing bacteria showing resistance to most antibiotics [9].

It is essential to consider the local microbial environment and resistance pattern as well as risk factors for harboring resistant microbes in individual patients. There is a direct correlation between the use of antibiotics and resistance development. There is an urgent need to combat resistance development by a prudent use of available antibiotics.

The current guidelines aim to provide both urologists and physicians from other medical specialties with evidence-based guidance regarding the treatment of UTI. High-quality clinical research using strict internationally recognized definitions and classifications as presented in this section is encouraged.

Level of evidence.

1a: Systematic reviews (with homogeneity) of randomized controlled trials.

1b: Randomized controlled trials.

1c: All or none randomized controlled trials.

2a: Systematic reviews of cohort studies.

2b: Individual cohort study or low quality randomized controlled trials.

2c: “Outcomes” Research; ecological studies.

3a: Systematic review of case-control studies.

3b: Individual case-control study.

4: Case-series.

5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles".

Recommendation grade:

Abbreviations: ESBL, extended-spectrum β-lactamase; UTI, urinary tract infection; CRP, C-reactive protein; TDM, therapeutic drug monitoring; CT, computed tomography; DMSA, dimercaptosuccinic acid; AAUS, Asian Association of UTI & STI.

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Table 1
Oral therapy in mild and moderate cases.

Antibiotics	Daily dose	Duration
Ciprofloxacin[a]	500 mg bid or 1000 mg qd	7–10 days
Levofloxacin[a]	500–750 mg qd	7–10 days
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)		
Ceftibuten	400 mg qd	10 days
Ceftitoren pivoxil	200 mg tid	14 days
Only if the pathogen is known to be susceptible (not for initial empirical therapy)		
Trimethoprim-sulfamethoxazole	160/800 mg tid	14 days
Amoxicillin/Clavulanic acid	875-2000/125 mg bid	14 days

[a] Lower dose studied, but higher dose recommended by experts.

Table 2
Initial parenteral therapy in severe cases.

Antibiotics	Daily dose
Cefotaxime[1)]	2 g tid
Ceftriaxone[2)]	1–2 g qd
Ceftazidime[1)]	1–2 g tid
Cefepime[12)]	1–2 g bid
Ampicillin/sulbactam	6 g bid~12 g eod
Piperacillin/tazobactam	4.5 g tid
Ceftolozane/tazobactam	1.5 g tid
Ceftazidime/avibactam	2.5 g tid
Ertapenem[2)]	1 g qd
Imipenem/cilastatin[2)]	0.5/0.5 g tid
Meropenem[2)]	0.5 g tid or eod
Doripenem[2)]	0.5 g tid
Gentamicin[1)]	5 mg/kg qd
Amikacin[1)]	200 mg qd

1) Not studied as monotherapy in acute uncomplicated pyelonephritis.
2) Same protocol for acute uncomplicated pyelonephritis and complicated UTI.

A: high.
B: moderate.
C: low.
D: very low.

The levels of evidence levels (LE) of cited article were determined according to the Outline for Preparation of Guidelines established by the Centre for Evidence-Based Medicine, Oxford [10]. The modified GRADE methodology [11] was used for grading the recommendations.

2. Executive summary

Epidemiology and pathogenesis.

1. Classification and characteristics of the disease: Pyelonephritis is the inflammation of the renal parenchyma and renal pelvis by ascending infection from the urinary tract. Renal tissue destruction spreads to the parenchyma and easily induces sepsis or bloodstream infection (LE:3). It is classified as either acute uncomplicated UTI or complicated UTI with an underlying disease.
2. Spectrum and frequency of causative organisms: The spectrum of etiological bacteria is similar in uncomplicated upper and lower UTIs, with *Escherichia coli* the causative pathogen in about 80% of cases (LE: 2a).

2.1. Treatments

1. Principles of antimicrobial therapy: Renal excretion typed antibiotics such as β-lactams and quinolones are recommended (LE:1a, GR:A).
2. De-escalation: The effect of empirical therapy must be determined three days after the start of treatment. Then, once the patients state of infectious diseases becomes better and controlled, in accordance with bacterial culture and antimicrobial susceptibilities, it is necessary to switch to definitive therapy (LE:2a, GR:A).
3. Switch therapy: Once the patients state of infectious diseases becomes better and controlled, we recommend switching from parenteral antimicrobial agents to oral medications such as antipyretics by around 24 h after symptom remission (LE:1a, GR:A).
4. Add on therapy: An oral agent is selected as the first line chemotherapy for outpatients with mild or moderate acute uncomplicated pyelonephritis. However, combination with a single injection drug at the first visit is also recommended (LE:1a, GR:A).
5. Severe conditions: When we find special conditions such as hydronephrosis, abscess formation and gas production, we must diagnose accurately and quickly, and perform urological procedures to preserve renal function and additional treatment or prevent patients' condition (LE:2a, GR:A).
6. Combination therapy: We recommend combination therapy in more severe pyelonephritis cases with urosepsis or septic shock (LE:2a, GR:A).

(Figures 1 and 2)

7. Recommendation (Summary)
(Pre- and post-menoposal women)

Mild and moderate cases:

- Ciprofloxacin 500 mg bid or 1000 mg qd 7–10 days[1)]
- Levofloxacin 500–750 mg qd 7–10 days[1)]
  1) It is not recommended in the following case: 1) the region where the resistant rate of E. coli to fluoroquinolones is 20% or higher, and 2) the patients who took fluoroquinolones within 6 months.

From the finding of urinary microscopic examination, fluoroquinolones is recommended in the case of gram positive cocci and cephalosporins is in the case of gram negative rods.

Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)

- Ceftibuten 400 mg qd 10 days
- Cefditoren pivoxil 200 mg tid 14 days

Only if the pathogen is known to be susceptible (not for initial empirical therapy)

- Trimethoprim-sulfamethoxazole 160/800 mg tid 14 days
- Amoxicillin/Clavulanic acid 875–2000/125 mg bid 14 days

Severe cases: The initial parenteral therapy in severe cases.

- Cefotaxime[1)] 2 g tid
- Ceftriaxone[2)] 1–2 g qd
- Ceftazidime[1)] 1–2 g tid
- Cefepime[2)] 1–2 g bid
- Ampicillin/sulbactam 6 g bid~12 g eod
- Piperacillin/tazobactam 4.5 g tid
- Ceftolozane/tazobactam 1.5 g tid
- Ceftazidime/avibactam 2.5 g tid
- Ertapenem[2)] 1 g qd
- Imipenem/cilastatin[2)] 0.5/0.5 g tid
- Meropenem[2)] 0.5–1 g tid or eod
- Doripenem[2)] 0.5 g tid
- Gentamicin[1)] 5 mg/kg qd
- Amikacin[1)] 200 mg qd

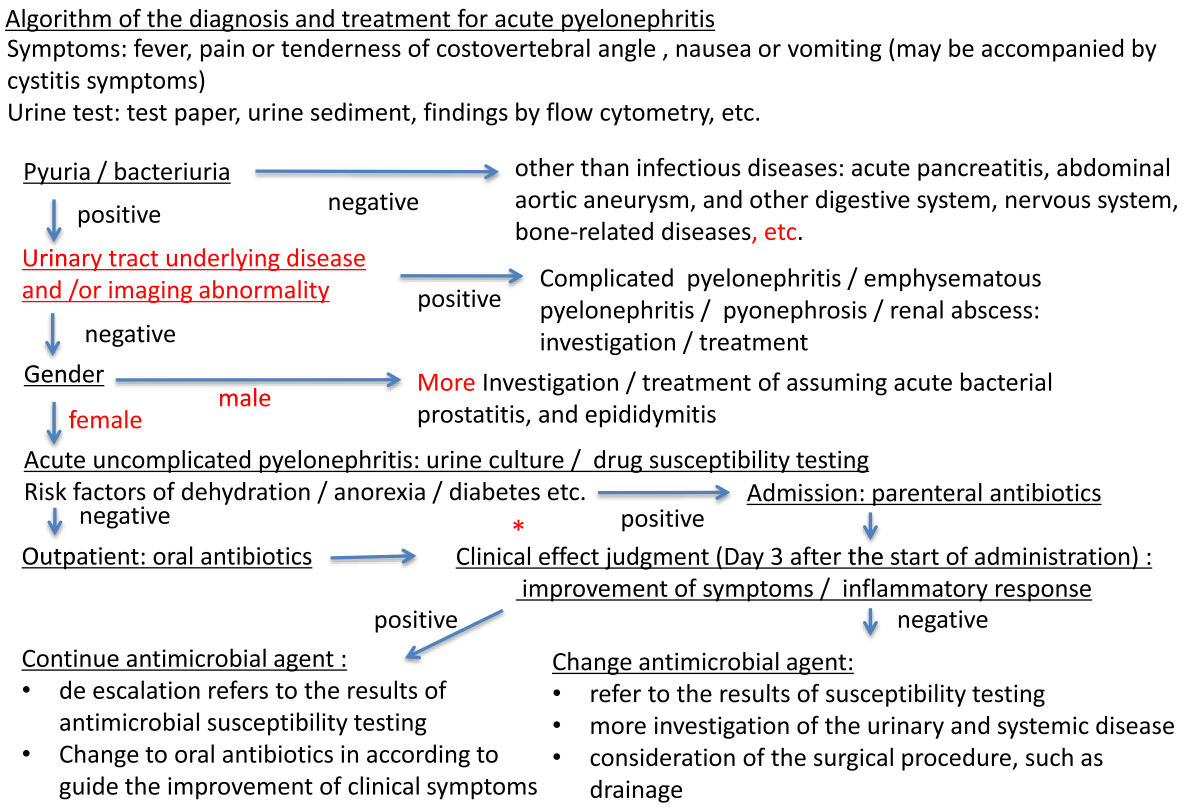

Fig. 1. Algorithm for diagnosis and treatment of acute uncomplicated pyelonephritis.

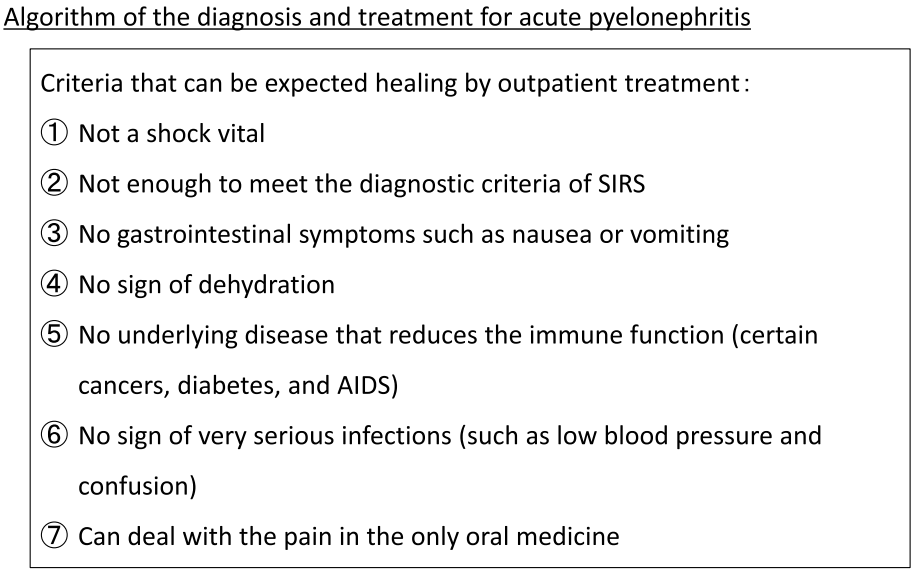

Fig. 2. There are 7 categories where the patients with acute pyelonephtritis do not necessarily hositalize and are considred as outpatients for the tretaments.

1) Not studied as monotherapy in acute uncomplicated pyelonephritis.
2) Same protocol for acute uncomplicated pyelonephritis and complicated UTI

Pregnant patients: mild or moderate cases:

- Ceftibuten 400 mg qd 10 days
- Cefditoren pivoxil 200 mg tid 14 days

*one—time intravenous agent by intravenous Ceftriaxone at the initiation of oral antimicrobial agents is recommended.

Severe cases:

- Ceftazidime 1-2 g tid
- Ceftriaxone 1-2 g qd or bid

3. Epidemiology

Sexually active women are at risk for acute uncomplicated pyelonephritis. All male patients with acute pyelonephritis (or UTI) are treated as complicated pyelonephritis (or UTI)."

The spectrum of antimicrobial agents is similar in uncomplicated upper and lower UTIs, with *Escherichia coli* the causative pathogen in 70–95% of cases [12,13]. Occasionally, other *Enterobacteriaceae*, such as *Proteus mirabilis* and *Klebsiella* spp., are isolated [14] (LE: 2a). There are several Asian studies about antimicrobial susceptibility in UTI. In Korean 10-years UTI study, strains showed relatively high resistance rate to fluoroquinolone (ciprofloxacin 54.9%, levofloxacin 39.0%), and cephalosporin (42%; 42.5–49.4%). On the other hands, uropathogens had maintained the highest level of susceptibility to amikacin and imipenem (24.9% and 11.3% resistance rates, respectively) [15].

And Nepal study showed that *Escherichia coli* (77.8%) and *Klebsiella pneumoniae* (14.8%) were common among the uropathogens. Strains showed high resistant rate to amoxicillin (80.3%) and cotrimoxazole (51.2%), whereas most of them were susceptible to amikacin, nitrofurantoin, and ofloxacin. Multi-drug resistant(MDR) was detected in 34.5% and Extended-spectrum β-lactamase (ESBL) producers in 24.6% of them. They reported the proportion of MDR isolates was higher in children $<$ 5 years (38.6%) than children $\geq$ 5 years (22%) (p= 0.03) [16].

In addition, Japanese study reported 181 GNR strains as UTI causative agents, and most of them were *Escherichia coli* (75%). Forty strains (22%) were exhibited third-generation cephalosporin resistance, and 63% of them were *E.coli*. Overall susceptibility rate of Enterobacterales was 92%, 81%, 100%, 75%, and 89% for cefmetazole, ceftriaxone, meropenem, levofloxacin, and trimethoprim-sulfamethoxazole, respectively. They reported residence in a nursing home and recent antibiotic use were independent risk factors for UTI with resistant GNR [17].

Moreover, *E. coli* (60.5%) and *K. pneumoniae* (16.0%) were the major UTI pathogens in Chinese study during 2016–2017. Five hundred fifty-four (47.0%) of 1178 *E. coli* isolates and 109 (32.9%) of 311 *K. pneumoniae* isolates from UTI produced ESBL, and they showed high susceptible rate to amikacin (94.7%, 88.4%), imipenem (97.0%, 87.5%), and ertapenem (91.4%, 82.1%), respectively [18].

Since suitable surveillance studies are lacking, the spectrum and susceptibility patterns of uropathogens that cause uncomplicated cystitis can be used as a guide for empirical therapy [19] (LE: 4, GR: B). However, *S. saprophyticus* is less frequent in acute pyelonephritis as compared to acute cystitis (LE: 4, GR: B).

4. Diagnostic criteria

4.1. Clinical symptoms

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever >38 °C and general malaise, and it can occur in the absence of symptoms of cystitis [20].

4.2. Physical examination

Costovertebral angle tenderness of the affected side is often seen.

4.3. Laboratory investigation

Urinalysis, including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis [21] (LE: 4, GR: C). Uropathogen colony counts $>10^4$ cfu/mL are considered to indicate clinically relevant bacteriuria [22] (LE: 2b, GR: C). A urine culture test is essential for proof of the causative bacteria and to determine drug susceptibility. In blood examination, inflammatory findings such as leukocytosis, left-shifted nuclear, elevation of CRP [23–25], elevated procalcitonin [25] and an elevated sedimentation rate can be seen.

If bacteremia is suspected, blood culture tests are necessary, especially in situations of suspected sepsis [26]. This may be accompanied by a state of shock, and attention should be paid to hemodynamics [27].

4.4. Radiological investigation

Evaluation of the upper urinary tract with ultrasound should be performed to rule out urinary tract obstruction or renal stone disease (LE: 4, GR: C).

Additional investigations, such as enhanced helical CT, excretory urography or DMSA scanning, should be considered if the patient remains febrile after 72 h of treatment (LE: 4, GR: C).

Enhanced abdominal CT is also useful in the differential diagnosis of emphysematous pyelonephritis, pylonephrosis, renal abscess, and acute uncomplicated pyelonephritis [28].

5. Treatments

5.1. Medication

In patients suspected of having pyelonephritis, a urine culture and antimicrobial susceptibility test should always be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen (LE:3, GR:A).

Mild and moderate cases are indicated as patients not requiring hospitalization and severe cases are indicated as women with pyelonephritis requiring hospitalization [27].

For the treatment of acute pyelonephritis, renal excretion typed antibiotics such as β-lactams [29] or fluoroquinolones [30,31] are recommended in the case of no apparent presence of resistant bacteria to β-lactams or fluoroquinolones (LE; 1, GR:A). The safety margin of aminoglycosides is so narrow that patients with renal dysfunction require close attention (LE:4, GR:B). If necessary, TDM is recommended.

5.2. Mild and moderate cases of acute uncomplicated pyelonephritis (Pre- and post-menoposal women)

In mild and moderate cases of acute uncomplicated pyelonephritis, oral therapy for 7–14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7–14 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still <10% [32] (LE: 1b, GR: A). If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5–7 days [33,34] (LE: 1b, GR: B). However, increasing numbers of fluoroquinolone-resistant *E. coli* have already been found in some Asian countries, and this restricts the empirical use of fluoroquinolones [8].

If an initial one-time intravenous agent is used, long-acting antimicrobials, such as 1 g of ceftriaxone or a consolidated 24 h dose of an aminoglycoside could be used in lieu of an intravenous fluoroquinolone (LE: 3, GR: B). If the prevalence of fluoroquinolone resistance is thought to exceed 10%, 1 g of ceftriaxone or aminoglycoside is recommended as an initial one-time intravenous agent (LE: 3, GR: B). This is because the emergence of fluoroquinolone-resistant Enterobacteriaceae is thought [35]. (i. Data are insufficient to make a recommendation about what fluoroquinolone resistance level requires an alternative agent in conjunction with or to replace a fluoroquinolone for treatment of pyelonephritis.) A third-generation oral cephalosporin, such aseftibuten, or cefditoren pivoxil could be an alternative [36,37] (LE: 1b, GR: B). However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin.

Guidelines' recommendations are only partially concordant with such findings and not supported by high quality evidence. Indeed, they recommend different treatments duration depending on the severity of disease and the type of antibiotic used: for mild/moderate uncomplicated pyelonephritis 5–10 days of treatment with a fluoroquinolone,

7–10 days with a 3rd generation oral cephalosporin and 10–14 days with trimethoprim-sulfamethoxazol or penicillin. These recommendations are considered to be supported by a moderate to good level of evidence. Nevertheless, only few RCTs included in our meta-analysis are cited by the guidelines, and there is low concordance between the citations provided by the different guidelines.

Oral β-lactam agents are often less effective than other available agents for treatment of pyelonephritis (LE: 3, GR: B). If an oral β-lactam agent is used, an initial intravenous long-acting antimicrobial agent (LE: 2, GR: B) or a consolidated aminoglycoside is recommended (LE: 3, GR: B). (i. Data are insufficient to modify the previous guideline recommendation for a duration of therapy of 10–14 days for treatment of pyelonephritis with a β-lactam agent including penicillins with β-lactamase inhibitors such as Amoxicillin/Clavulanic acid (AMPC/CVA) 0.875–2/0.125g bid for 14 days [5].

Oral trimethoprim-sulfamethoxazole (160/800 mg [1 double-strength tablet] twice-daily for 14 days) is an appropriate choice for therapy if the uropathogen is known to be susceptible (LE: 1, GR: A). If trimethoprim-sulfamethoxazole is used when the susceptibility is not known, an initial intravenous long-acting antimicrobial agent (LE: 2, GR: B) or a consolidated aminoglycoside is recommended (LE: 3, GR: B) [38].

5.3. Severe cases of acute uncomplicated pyelonephritis (Pre-and post-menoposal women)

Patients with severe pyelonephritis who cannot take oral medication because of systemic symptoms such as nausea and vomiting have to be treated initially with one of the following parenteral antibiotics.

Women with pyelonephritis requiring hospitalization should be initially treated with an intravenous antimicrobial regimen, such as a fluoroquinolone; an extended-spectrum cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside; or a carbapenem. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results (LE: 3, GR: B). And recently newer cephalosporins with beta-lactamase inhibitors. Ceftolozane-tazobactam has been recently commercially available and could be a choice for this category treatments [39].

Hospital admission should be considered if complicating factors cannot be ruled out by available diagnostic procedures and/or the patient has clinical signs and symptoms of sepsis (LE: 4, GR: B).

After improvement, the patient can be switched to an oral regimen using one of the above-mentioned antibacterials, if active against the infecting organism, to complete the 1–2 week course of therapy (LE: 1b, GR: B).

For severe uncomplicated pyelonephritis guideline by Bonkat et al. [35] and by Kranz et al. [40] suggested to complete a course of 1 or 2 weeks of antibiotic treatment.

In communities with high rates of fluoroquinolone-resistant and ESBL-producing *E. coli* (>10%), initial empirical therapy with carbapenems or broad spectrum cephalosporins or penicillins including beta-lactamase inhibitors [41–46] has to be considered until susceptibility testing demonstrates that oral drugs can also be used (LE: 4, GR: B).

5.4. For pregnant patients [35]

Patients of pregnant women should be especially paid attention and needs some consideration including not only recommendation but contraindication. We have shown them as follows. In mild or moderate cases, Ceftibuten or Cefditoren pivoxil are used but one—time intravenous agent by intravenous Ceftriaxone at the initiation of oral antimicrobial agents is recommended. In severe cases, Ceftazidime 1–2 g or Ceftriaxone 1–2 g are used as mentioned above.

5.5. Caution for contraindication for pregnant patients

The antimicrobial agents such as fluoroquinolones, aminoglycosides, tetracycline, Sulfamethoxazole - Trimethoprim and sulfonamides are not recommended for pregnant patients according to FDA categorization (Category C or D) [47–49].

5.6. Follow up

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C). In women whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal ultrasound, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

In patients with no urological abnormality, it should be assumed that the infecting organism is not susceptible to the agent originally used, and an alternative tailored treatment should be considered based on culture results (LE: 4, GR: B). For patients who relapse with the same pathogen, the diagnosis of uncomplicated pyelonephritis should be reconsidered. Appropriate diagnostic steps are necessary to rule out any complicating factors (LE: 4, GR: C).

6. Future research

There are no prospective studies with larger cohort or randomized-control studies to evaluate appropriate management strategies for uncomplicated pyelonephritis. However, as mentioned above, oral 3rd generation cephalosporines have not been recommended for this infectious disease category owing to their low bioavailability. Further evidence is needed for definitive evaluation.

7. Conclusions

European guidelines have introduced newly-established broad-spectrum antibiotics including beta-lactamase inhibitors. This implies that uncomplicated pyelonephritis is no longer considered a “safe” disease since it can lead to sepsis. Further prospective research in Asian populations is necessary for definitive conclusions.

8. ICMJE authorship criteria

Authorship All authors meet the ICMJE authorship criteria. Shigemura K and Ishikawa K designed this study. All other authors collected the data and reviewed the manuscript. All authors have approved the submission of this version of the manuscript.

References

[1] Grabe M, Bartoletti R, Bjerklund-Johansen TE, Cek HM, Pickard RS, Tenke P, et al. Guidelines on urological infections. European Association of Urology; 2014. p. 8–19. UPDATE.

[2] Naber KG, Wullt B, Wagenlehner FME. Antibiotic treatment of uncomplicated urinary tract infection in premenopausal women. Stockholm, Sweden: Urogenital Infections. International Consultation on Urogenital Infections; 2009. p. 171–99. EAU Edition 2010.

[3] Gupta K, Hooton TH, NaberKG. International clinical guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious disease society of America and the European society for microbiology and infectious diseases. Clin Infect Dis 2011;52:103–20.

[4] Gilbert DN, Moellering RC, Eliopoulos GM, et al. Kidney bladder and prostate. 44TH Edition. The Sanford Guide to Antimicrobial Therapy; 2014. p. p34–35. 2014.

[5] Aoki N, Arakawa S, Ouchi K, Kiyota H, Tateda K, Mikasa K, et al. The JAID/JSC guide to clinical management of infectious disease 2011. Japan: Life science shuppan KK; 2012 March.

[6] Carlet J, Collignon P, Goldmann D, et al. Society’s failure to protect a precious resource: antibiotics. Lancet 2011;378(9788):369–71.

[7] Gyssens IC. Antibiotic policy. Int J Antimicrob Agents 2011;38(Suppl):11–20.

[8] Shin J, Kim J, Wie SH, Cho YK, Lim SK, Shin SY, et al. Fluoroquinolone resistance in uncomplicated acute pyelonephritis:epidemiology and clinical impact. Microb Drug Resist 2012;18:169–75.
[9] Oteo J, Pérez-Vázquez M, Campos J. Extended-spectrum [beta]-lactamas producing Escherichia coli: changing epidemiology and clinical impact. Curr Opin Infect Dis 2010;23:320–6.
[10] Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995–8.
[11] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[12] Schit GC, Naber KG, Botto H, et al. An international survey on the antimicrobial resistance of pathogen involved in uncomplicated urinary tract infection. Int J Antimicrob Agents 2009;34:407–13.
[13] Naber KG, Schito G, Botto H, et al. Surveillance study in europe and Brazil on clinical aspects and antimicrobial resistance epidemiology in females with cystitis (ARESC): implications for empiric therapy. Eur Urol 2008;54:1164–75.
[14] Wong CKM, Kung K, Au-Doung PLW, Ip M, Lee N, Fung A, et al. Antibiotic resistance rates and physician antibiotic prescription patterns of uncomplicated urinary tract infections in southern Chinese primary care. PLoS One 2017 May 9;12 (5):e0177266.
[15] Choe HS, Lee SJ, Cho YH, Çek M, Tandoğdu Z, Wagenlehner F, et al. GPIU Asian Investigators. Aspects of urinary tract infections and antimicrobial resistance in hospitalized urology patients in Asia: 10-Year results of the Global Prevalence Study of Infections in Urology (GPIU). J Infect Chemother 2018 Apr;24(4):278–83.
[16] Raya GB, Dhoubhadel BG, Shrestha D, Raya S, Laghu U, Shah A, et al. Multidrug-resistant and extended-spectrum beta-lactamase-producing uropathogens in children in Bhaktapur, Nepal. Trop Med Health 2020 Aug 3;48:65.
[17] Kanda N, Hashimoto H, Sonoo T, Naraba H, Takahashi Y, Nakamura K, et al. Gram-negative organisms from patients with community-acquired urinary tract infections and associated risk factors for antimicrobial resistance: a single-center retrospective observational study in Japan. Antibiotics (Basel) 2020 Jul 23;9(8): 438.
[18] Zhang H, Johnson A, Zhang G, et al. Susceptibilities of Gram-negative bacilli from hospital- and community-acquired intra-abdominal and urinary tract infections: a 2016–2017 update of the Chinese SMART study. Infect Drug Resist 2019 Apr 24; 12:905–14.
[19] Kim KS, Kim K, Jo YH. A simple model to predict bacteremia in women with acute pyelonephritis. J Infect 2011;63:124–30.
[20] Fulop T. Acute pyelonephritis workup. Aug 22 [Access date February 2014], http://emedicine.medscape.com/article/245559-workup#aw2aab6b5b3; 2012.
[21] Rubin US, Andriole VT, Davis RJ, et al. Evaluation of new anti-infective drugs for the treatment of UTI. Clin Infect Dis 1992;15:216.
[22] Yang WJ, Cho IR, Seong do H, Song YS, Lee DH, Song KH, et al. Clinical implication of serum C-reactive protein in patients with uncomplicated acute pyelonephritis as marker of prolonged hospitalization and recurrence. Urology 2009;73:19–22.
[23] Yasufuku T, Shigemura K, Yamashita M. Selection of first-line i.v.antibiotics for acute pyelonephritis in patient required emergency hospital admission. J Infect Chemother 2011;14:231–7.
[24] Claessens YE, Schmidt J, Batard E, et al. Can C-reactive protein, procalcitonin and mid-regional pro-atrial natriuretic peptide measurements guide choice of in-patients or out-patients care in acute pyelonephritis? Biomarkers In Sepsis (BIS) multicentrestudy. Clin Microbiol Infect 2010;16(6):753–60.
[25] Etienne M, Van Elslande H, Choplin-Renard J, Pestel-Caron M, Caron F. Antibiotic resistance in adult female patients hospitalized for acute pyelonephritis: rates and predicting factors. Med Maladies Infect 2014;44:217–22.
[26] Singer M, Deutschman CS2, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.
[27] Scholes D, Hooton TM, Roberts PL, et al. Risk factors associated with acute pyelonephritis in healthy women. Ann Intern Med 2005;142:20–7.
[28] Takahashi S, Kurimura Y, Takeyama K. Efficacy of treatment with carbapenemes and third-generation cephalosporins for patients with febrile complicated pyelonephritis. J Infect Chemother 2009;15:390–5.
[29] Jeon JH, Kim K, Han WD, et al. Empirical use of ciprofloxacin for acute uncomplicated pyelonephritis caused by Escherichia coli in communities where the prevalence of fluoroquinolone resistance is high. Antimicrob Agents Chemother 2012;56:2043–3046.
[30] Sandberg T, Skoog G, HermanssonAB. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomized, open label and double-blind, placebo-controlled, non-inferiority trial. Lancet 2012;380(9840):484–90.
[31] Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprimsulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA 2000;283:1583–90.
[32] Klausner HA, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Curr Med Res Opin 2007;23:2637–45.
[33] Peterson J, Kaul S, Khashab M, et al. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology 2008;71:17–22.
[34] Matsumoto T, Yamaguchi H, Uchino K, et al. Efficacy and safety of sitafloxacin in patients with urinary tract infections. Jpn J Antibiot 2012;65:365–80.
[35] JAID/JSC guide for infectious diseases. Pyelonephritis; 2019.
[36] Naber KG, Schoenwald S, Hauke W. Cefpodoximeproxetil in patients with acute uncomplicatedpyelonephritis. International, prospective, randomized comparative study versus ciprofloxacin ingeneral practice. Chemother J 2001;10:29–34.
[37] Bader MS, Loeb M, Leto D, Brooks AA. Treatment of urinary tract infections in the era of antimicrobial resistance and new antimicrobial agents. Postgrad Med 2019 Oct 24:1–17.
[38] Bonkat G, Pickard R, Bartoletti R, et al. EAU guidelines on urological infections. 2017.
[39] Arakawa S, Kawahara K, Kawahara M, Yasuda M, Fujimoto G, Sato A, et al. The efficacy and safety of tazobactam/ceftolozane in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection. J Infect Chemother 2019;25:104–10.
[40] Kranz J, Schmidt S, Lebert C, et al. The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients Part II: therapy and prevention. Urol Int 2018;100(3):271–8. https://doi.org/10.1159/000487645.
[41] Lee SS, Kim Y, Chung DR. Impact of discordant empirical therapy on outcome of community-acquired bacteremic acute pyelonephritis. J Infect 2011;62:159–64.
[42] Wells WG, Woods GL, Jiang Q, et al. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by an appropriate oral therapy. J Antimicrob Chemother 2004;53(Suppl 2):ii67–74.
[43] Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. Meropenem Study Group. J Antimicrob Chemother 1995;36 (Suppl A):145–56.
[44] Giamarellou H. Low-dosage cefepime as treatment for serious bacterial infections. J Antimicrob Chemother 1993;32(Suppl B):123–32.
[45] Naber KG, Savov O, Salmen HC. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/cilastatin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents 2002;19:95–103.
[46] Naber KG, Llorens L, Kaniga K, et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for the treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother 2009;53:3782–92.
[47] United States Food and Drug Administration. Labeling and prescription drug advertising: content and format for labeling for human prescription drugs. Fed Regist 1979;44:37434–67.
[48] Briggs GGFR. Drugs in pregnancy and lactation. Baltimore, MD: Williams and Wilkins; 2014.
[49] United States National Library of Medicine. DailyMed. Available from, http://dailymed.nlm.nih.gov/dailymed/index.cfm. [Accessed 27 April 2015].