

Efficacy of Additional Solifenacin Succinate Therapy for Storage Symptoms in Females with Uncomplicated Lower Urinary Tract Infection: The SOLUTION Randomized Controlled Trial

Harrina E. Rahardjo, Firtantyo A. Syahputra, Putri I. Islianti,
Faisal A. Matondang

Department of Urology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:

Harrina Erlianti Rahardjo, MD., PhD. Department of Urology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71 Jakarta 10430, Indonesia. email: harrinaerlianti@gmail.com.

ABSTRAK

Latar belakang: infeksi saluran kemih (ISK) sering ditangani dalam praktek sehari-hari sebagai overactive bladder (OAB) dengan memberikan antikolinergik yaitu pilihan pengobatan yang direkomendasikan untuk OAB. Namun aplikasi antikolinergik untuk menghilangkan gejala ISK belum pernah diteliti. Sepengetahuan kami, penelitian ini merupakan uji klinis pertama yang menyelidiki penggunaan antikolinergik dalam pengobatan ISK. Penelitian ini bertujuan mengevaluasi apakah terapi tambahan antikolinergik bersama antibiotik empiris bermanfaat mengurangi gejala dan aman bagi wanita dengan ISK non-komplikata. **Metode:** penelitian ini berupa uji acak terkendali tersamar ganda terhadap wanita berusia >18 tahun dengan ISK non-komplikata. Pasien diacak untuk menerima solifenacin succinate 5 mg (kelompok 1) atau plasebo (kelompok 2) sebagai tambahan terhadap terapi empiris levofloxacin 500 mg selama 3 hari. Pasien dengan kelainan struktural dan/atau fungsional, dan dengan riwayat reaksi alergi dieksklusi dari penelitian. Kami mengamati perubahan overactive bladder symptom score (OABSS), skor patient perception of bladder condition (PPBC), gejala lain yang dilaporkan pasien, serta efek samping yang dialami. **Hasil:** sebanyak 126 pasien, 63 untuk masing-masing kelompok, memulai penelitian ini dengan median usia 44 (19-67) tahun. Tidak didapatkan perbedaan usia, OABSS, dan skor PPBC di antara kedua kelompok pada awal penelitian. Kedua kelompok menunjukkan penurunan bermakna ($p<0,05$) OABSS dan skor PPBC di akhir terapi; namun besar penurunan di antara keduanya tidak berbeda. Pada kelompok 1 didapatkan 22,2% pasien mengeluhkan mulut kering, 3,2% konstipasi, 25,4% mual, dan 4,7% mengantuk. Pada kelompok 2 didapatkan 20,0% pasien mengeluhkan mulut kering, 21,7% mual, dan 3,3% mengantuk. Satu pasien pada kelompok 2 mengalami reaksi alergi sehingga dikeluarkan dari penelitian. **Kesimpulan:** tidak didapatkan perbedaan bermakna penurunan OABSS dan skor PPBC dengan menambahkan antikolinergik bersama antibiotik empiris pada wanita dengan ISK non-komplikata. Tidak ditemukan adanya efek samping serius pada studi ini.

Kata kunci: skor overactive bladder symptom (OABSS), patient perception of bladder condition (PPBC), solifenacin succinate, ISK tanpa komplikasi.

ABSTRACT

Background: urinary tract infection (UTI) is often treated in daily practice as overactive bladder (OAB) by giving anticholinergic, the recommended treatment options of OAB. However, anticholinergic application for UTI symptoms relief has never been investigated. To our knowledge, this study was the first randomized trial which investigate anticholinergic use for UTI treatment. This study aimed to evaluate whether additional anticholinergic

is beneficial alongside an empiric antibiotic therapy in reducing symptoms and tolerable for females with uncomplicated UTI. **Methods:** this was a randomized double-blind controlled trial that included female aged >18 y.o with uncomplicated lower UTI. Patients were randomly assigned to either solifenacin succinate 5 mg (group 1) or placebo (group 2) in addition to empiric levofloxacin 500 mg treatment for 3 days. Those with structural and/or functional abnormalities of the urinary tract and allergic reaction history were excluded. We observed changes in overactive bladder symptom score (OABSS), patient perception of bladder condition (PPBC) score, patient-reported symptoms and adverse events. **Results:** a total of 126 patients, 63 for each group, initiated the trial with median age of 44 (19-67) y.o. There were no differences of age, OABSS, and PPBC score between the 2 groups at baseline. We found significant ($p<0.05$) reduction of OABSS and PPBC score in both groups at the end of therapy; however the amount of reduction were not different between groups. In group 1 we found 22.2% of patients complained of dry mouth and 25.4%, 4.7%, 3.2% of patients complained of nausea, somnolence and constipation respectively. In group 2 we found 20.0%, 21.7% and 3.3% patients who complained of dry mouth, nausea, and somnolence respectively. One patient in group 2 experienced allergic reaction and was dropped out. **Conclusion:** we found no significant difference in OABSS and PPBC score reduction by adding anticholinergic to antibiotic therapy for females with uncomplicated UTI. There was no serious adverse event recorded.

Keywords: overactive bladder symptom score (OABSS), patient perception of bladder condition (PPBC), solifenacin succinate, uncomplicated UTI.

INTRODUCTION

Urinary tract infection (UTI) is a common health problem for females in which half of them suffered from it once in a lifetime.^{1,2} It becomes the most common non-intestinal infection suffered by females worldwide,³ while in developing countries its prevalence varies between 10-40%.^{4,5} Acute uncomplicated lower UTI was frequently found in healthy, non-pregnant, adult female with no other anatomical or functional abnormalities of the urinary tract.⁶ In spite of its low morbidity, uncomplicated UTI may result in daily activity disturbance² and cost burden.⁷

Empiric antibiotics remain as standard treatment for uncomplicated UTI with bothersome urinary tract symptoms and has been reported to be cost-effective.⁸ Nevertheless, in some patients the symptoms are not relieved at the end of treatment. UTI Symptoms (e.g. dysuria, frequency, urgency), which mimic the storage symptoms of overactive bladder (OAB), sometimes remain to interfere with women's daily routines. Several treatment strategies aside from extending antibiotic duration have been proposed to deal with UTI symptoms without rising resistance.⁹ Due to its similar symptoms, UTI is often treated in daily practice as OAB by giving anticholinergic, the recommended treatment options of OAB.¹⁰ However anticholinergic

application for UTI symptoms relief has never been investigated. To our knowledge, this study was the first randomized trial which investigate anticholinergic use for UTI treatment.

We aimed to evaluate whether additional anticholinergic therapy alongside an empiric antibiotic therapy is beneficial and tolerable in reducing symptoms in females with uncomplicated lower UTI.

METHODS

This trial recruited female aged more than 18 y.o with acute or recurrent uncomplicated lower UTI who came to our hospital's urology outpatient clinic. Diagnosis was made based on history of the disease, physical examination, and laboratory findings. A simple questionnaire sheet was used to record specific data, including age, duration of symptoms, episode of infection, and other comorbidities. We used overactive bladder symptom score (OABSS)¹¹ and patient perception of bladder condition (PPBC)¹² tools to assess severity of the symptoms. All patients were provided with clean urine container to collect midstream urine samples.

We diagnosed UTI in female who suffered from at least one of the symptoms (dysuria, urinary frequency, nocturia, urgency)¹³ accompanied with one of the following urinalysis criteria: five or more

white blood cells per high power field (HPF) on microscopic analysis,¹⁴ positive bacteria, positive nitrite or leucocyte-esterase test on dipstick.¹⁵ We ruled out those with indwelling catheter, pregnancy, history of urinary tract structural or functional abnormalities, preexisting disorder of the bladder (stone, mass), sexually transmitted disease (urethritis, vaginitis, genital herpes), neurologic disorder, and allergic reaction history toward levofloxacin or solifenacin succinate.

Study Outcome

We assessed OABSS and PPBC score before intervention began as baseline. Then OABSS and PPBC were measured each day during treatment and after completion of treatment. Patient-reported symptoms and adverse event were also noted. We observed changes in the OABSS and PPBC score compared to baseline.

Sample Size

Number of needed samples was calculated using statistical formula based on OABSS difference at the end of therapy between the two groups that is considered significant by the investigator (Δ OABSS = 2). Sixty patients of each groups were needed to achieve confidence interval of 95% and statistical power of 80%.

Randomization and Blind

Our study was a double blind randomized controlled trial, in which the evaluator did not know about the category of subject groups. The study participants were recruited by urologists or urology residents in duty. Eligible subjects were randomly assigned (1:1 ratio) with permuted block methods (block sizes 4) using online random number generator in sequentially concealed numbered envelopes to receive one of the following treatments orally once daily for a period of 3 days: solifenacin succinate 5 mg and levofloxacin 500 mg (group 1) or placebo and levofloxacin 500 mg (group 2). All the drugs were given in similar preparation. We used quinolone drug class to treat UTI according to antibiotic sensitivity pattern in our hospital.¹⁶ Patient and physician were blinded toward given drug.

Statistical Analysis

Data was analyzed using a computer software statistical program of SPSS version

22.0. Analysis was performed per protocol to compared group 1 versus group 2, for which the trial was powered at 95%. Chi-square analysis was used to compare proportion of marital status. When the data did not meet Chi-square criteria we used Fisher test. Bivariate numerical analyses of age, OABSS and PPBC score were performed using unpaired student t-test when the data in both groups showed normal distribution or mann-whitney rank test when it did not show normal distribution. We used paired sample t-test to compare OABSS and PPBC score changes in each groups between days, when distribution showed inhomogenous data we used wilcoxon test. The level of significance used was based on a two-sided $p < 0.05$.

Study Protocol

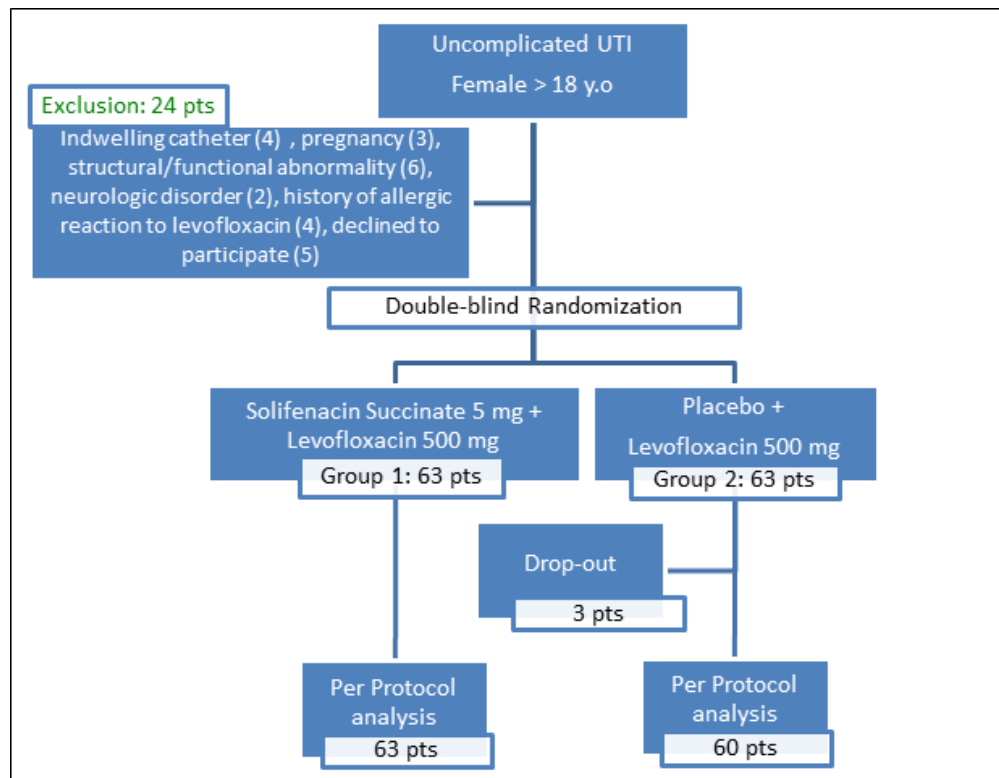
The consent to participate in the study was obtained by signing the written informed consent. This trial has been approved by Faculty of Medicine, Universitas Indonesia / Cipto Mangunkusumo Hospital Health Research Ethics Committee (574/PT02.FK/ETIK/2011) and registered at ClinicalTrials.gov (NCT02094703).

RESULTS

We randomized 63 patients into group 1 (anticholinergic and antibiotic) while another 63 patients were allocated into group 2 (placebo + antibiotic) as shown in **Figure 1**. There were no differences of age, marital status, level of education, OABSS and PPBC score between the two groups at baseline (**Table 1**). Three patients in group 2 were dropped out at final assessment (4 days after initial therapy). During the study there was one patient who refused to consume medication, one patient who lost the given drugs, while the third patient suffered from rash allergic reaction. Thus we performed per protocol analysis.

Frequency (53.2%) and urgency (46.8%) were the two most common symptoms suffered by the patients. Whereas only 8 (6.3%) patients who suffered from hematuria at initial presentation (**Table 1**).

Group 1 resulted in lower OABSS tendency compared to group 2 in all study day. A lower PPBC score was always found in group 1

**Figure 1.** Flowchart of the study**Table 1.** Baseline characteristics of the study population

Variables	Total (n=126)	Group 1 (n=63)	Group 2 (n=63)
Age* (years old), mean (SD); median (range)	42.18 (13.94); 44.00 (19.00-67.00)	43.16 (12.94); 45.00 (20.00-67.00)	41.21 (14.92); 42.00 (19.00-66.00)
Marital Status, n (%)			
- Married	99 (78.6)	53 (84.1)	46 (73.0%)
- Single	27 (21.4)	10 (15.9)	17 (27.0%)
Level of Education†, n (%)			
- Low	70 (55.6)	40 (63.5)	30 (47.6%)
- High	56 (44.4)	23 (36.5)	33 (52.4%)
OABSS*, mean (SD); median (range)	4.20 (3.97); 3.00 (0.00-20.00)	3.46 (3.12); 2.00 (0.00-11.00)	4.94 (4.57); 3.00 (0.00-20.00)
PPBC Score*, mean (SD); median (range)	1.88 (1.61); 2.00 (0.00-5.00)	1.73 (1.54); 1.00 (0.00-5.00)	2.03 (1.67); 2.00 (0.00-5.00)
Symptoms suffered, n (%)			
- Nocturia	53 (42.1)		
- Hematuria	8 (6.3)		
- Lower abdominal pain	45 (35.7)		
- Urgency	59 (46.8)		
- Frequency	67 (53.2)		
- Dysuria	53 (42.1)		

* Inhomogeneous

† Low education means high school or lower. High education means diploma degree or higher.

(Table 2). All the two groups showed significant ($p < 0.05$) reduction in OABSS and PPBC score at the end of therapy compared to baseline. Lower symptoms score reflects less symptoms suffered.

Significant OABSS and PPBC reduction in each groups were also found since the first day of treatment and continued until the end of observation. However, when we compare the reduction amount of OABSS and PPBC score before and after treatment, a non-significant results between the groups were shown (Table 2).

Adverse Event

In group 1 we found 22.2% patients who suffered from dry mouth and 25.4%, 4.7%, 3.2% of patients suffered from nausea, somnolence and

constipation respectively. There was no patient in group 1 who suffered from allergic reaction (Figure 2).

In group 2 we found 20.0%, 21.7% and 3.3% patients who suffered from dry mouth, nausea, and somnolence respectively. One patient in group 2 suffered from allergic reaction due to antibiotic then dropped out from the study. There was no patient in group 2 who suffered from constipation.

DISCUSSION

Uncomplicated UTI is considered as a rapid recovery disease. On the third day after doctors' treatment, most cystitis patients were free of

Table 2. Comparison of OABSS and PPBC score between groups based on day of treatment

	OABSS			PPBC Score		
	Group 1 (n=63)	Group 2 (n=60)	p value	Group 1 (n=63)	Group 2 (n=60)	p value
Initial*	3.46 (3.12) 2.00 (0.00-11.00)	4.94 (4.57) 3.00 (0.00-20.00)		1.73 (1.54) 1.00 (0.00-5.00)	2.03 (1.67) 2.00 (0.00-5.00)	
Day I*	2.30 (2.67) 1.00 (0.00-9.00)	3.33 (3.76) 2.00 (0.00-13.00)		1.25 (1.41) 1.00 (0.00-5.00)	1.70 (1.52) 2.00 (0.00-4.00)	
Day II *	1.65 (2.62) 1.00 (0.00-12.00)	2.73 (3.12) 1.00 (0.00-12.00)		0.92 (1.30) 0.00 (0.00-4.00)	1.38 (1.42) 1.00 (0.00-4.00)	
Day III *	1.18 (2.13) 0.00 (0.00-9.00)	2.25 (2.90) 1.00 (0.00-12.00)		0.68 (1.15) 0.00 (0.00-4.00)	1.07 (1.33) 0.00 (0.00-4.00)	
Day IV*	0.83 (1.74) 0.00 (0.00-9.00)	1.43 (2.43) 1.00 (0.00-11.00)		0.41 (0.93) 0.00 (0.00-4.00)	0.68 (1.17) 0.00 (0.00-4.00)	
Delta*	-2.63 (2.52) -2.00 (-8.00-1.00)	-3.55 (3.79) -2.00 (-19.00-1.00)	p = 0.293 (Mann-Whitney)	-1.32 (1.29) -1.00 (-4.00-0.00)	-1.37 (1.31) -1.00 (-4.00-0.00)	p = 0.864 (Mann-Whitney)

* Inhomogeneous

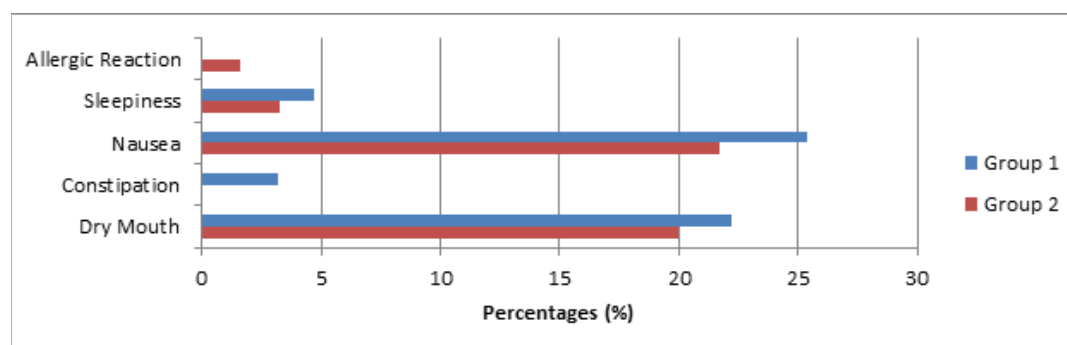


Figure 2. Proportion of adverse events

symptoms as shown in a Scandinavian study.¹⁷ Another study in Korean population reported a median of 2.40 days for symptoms improvement among simple cystitis patients after antibiotic treatment, however 15.3% patients were considered as failure of treatment.¹⁸ We proposed anticholinergic as an add-on therapy to empiric antibiotic in treating uncomplicated lower UTI. Anticholinergic was chosen considering its effect to reduce storage symptoms in OAB patients. Storage symptoms, one of the lower urinary tract symptoms (LUTS) spectrum, have been identified as bothersome symptoms in patients with UTI. Based on our knowledge this was the first study that analyzed utilization of anticholinergic for LUTS treatment caused by infection.

Antibiotic treatment is recommended in many guidelines to be given by primary care providers when someone was suspected with UTI.¹⁹⁻²¹ In our study levofloxacin was used as standard treatment. Fluoroquinolone is antimicrobial agent known for its broad spectrum activity against gram-positive and gram-negative bacteria.²² It works by trapping DNA gyrase and topoisomerase IV as complexes thus damaging DNA strands and inhibiting bacterial growth.²³

Bacterial colonization and inflammation of the urothelium was thought as etiology of LUTS in some women with UTI.²⁴ Storage LUTS were considered dominant in UTI patients. A study revealed that many molecular changes (increased purinergic signaling and high levels of NO) in bladder induced cystitis may lead to detrusor overactivity with lower bladder capacity, lower compliance, and decreased micturition interval.²⁵ Acute cystitis may result in 83.33% rate of detrusor instability in rat model study.²⁶ Inflamed bladder was found to induce hyperactivity and reduce micturition volume-pressure threshold.²⁷ An acute irritant infection increases the number of bladder mucosa and submucosa afferent C fibers thus enhanced sensitivity to incoming stimuli which manifested in frequent micturition, urgency, dysuria, and other LUTS.²⁶ It was shown that cystitis condition caused down-regulation of bladder muscarinic and purinergic receptors that related to cholinergic and purinergic nervous activity.²⁸

It has been suggested that anticholinergic inhibit the binding of acetylcholine, the primary contractile neurotransmitter at muscarinic receptors M2 and M3 on detrusor smooth muscle cells and bladder wall, eventually reduce spontaneous myocyte activity during storage phase. The results are decreasing in frequency and intensity of detrusor contractions.^{29,30} Those findings made anticholinergic a promising substance for UTI treatment. Solifenacin 5 mg was chosen as our main investigation subject since it showed the least adverse event in clinical practice,³¹ and its balance between efficacy and tolerability.³²

Different treatment strategies have been proposed to improve symptoms resolution.³³ A non-inferiority study showed that ibuprofen gives similar symptoms free results comparable with antibiotic. Ibuprofen was considered as an alternative treatment due to its analgesia and inflammatory activity.³⁴ Symptoms relieve became the target therapy for UTI since bacteriuria may remain asymptomatic.

Our study reported symptoms resolutions for both treatment arms after 3 days as shown in OABSS and PPBC score reduction. Even in the first day of treatment significant OABSS reduction were found in group 1 and 2: -1.16 and -1.65 respectively when compared to baseline. At the end of study, we found 58.7% patients in group 1 and 44.4% in group 2 did not have symptoms anymore. These results were similar to study conducted in Lower Saxony Germany which showed 51.5% completely free of symptoms patients after 3 days antibiotics treatment in women with uncomplicated UTI.³⁴ A Cochrane Database Systematic Review concluded that 3 days antibiotic therapy was considered enough to achieve symptomatic cure during uncomplicated UTI treatment in women while 5-10 days could be considered in obtaining bacteriological cure.³⁵ We found significant improvement in all urinalysis parameter including bacteriuria after 3 days treatment; unfortunately our tools did not enable to show quantitative assay.

This present study failed to show anticholinergic additional benefit in reducing storage symptoms induced by infection origin. Both group 1 and 2 showed significant reduction

of OABSS and PPBC score every day to the end of therapy, however when we compared derivation amount of each other the result was not significant. We think that this condition might be caused by self-limiting nature of uncomplicated UTI that made additional drug unnecessary. Another reason might be related to duration of anticholinergic administration until a therapeutic response emerges. A study in tertiary center in Taiwan toward OAB patients recorded 3 months median time was needed to show OABSS improvement;³⁶ while meta-analysis also indicated 12 weeks as time required to reduce the symptoms after initiating anticholinergic.³²

The most common adverse event to deal with anticholinergic consumption was gastrointestinal disorder;³¹ in our study we found 2 patients with constipation and 16 patients with nausea after one day treatment of solifenacin however these results did not differ significantly when compared to placebo group.

The weaknesses of our study are lack of non-antibiotic treatment arm, and no urine culture evidence. We suggest a further research conducted with similar scheme in patients with recurrent UTI or complicated UTI demanding a longer period of treatment. In those kinds of patients additional drugs might give more value.

CONCLUSION

In this study, we found no significant symptoms resolution as shown in no difference of OABSS and PPBC score reduction by adding anticholinergic to empiric antibiotic therapy compared to empiric antibiotic therapy alone for females with uncomplicated lower UTI. There was no serious adverse event recorded for adding anticholinergic to antibiotic therapy.

DATA ACCESS AND RESPONSIBILITY

The principal investigator had full access to all of the data and takes full responsibility for the integrity and accuracy of the analysis.

TRIAL REGISTRATION

This trial is registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02094703.

ACKNOWLEDGMENTS

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REFERENCES

1. Hummers-Pradier E, Kochen MM. Urinary tract infections in adult general practice patients. *Br J Gen Pract.* 2002;52:752-61.
2. Foxman B: Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med.* 2002;113 Suppl 1A:5S-13S.
3. Dielubanza EJ, Schaeffer AJ. Urinary tract infections in women. *Med Clin North Am.* 2011;95:27-41.
4. August SL, De Rosa MJ. Evaluation of the prevalence of urinary tract infection in rural Panamanian women. *PLoS One.* 2012;7:e47752.
5. Manjula NG, Math GC, Patil SA, Gaddad SM, Shivannavar CT. Incidence of urinary tract infections and its aetiological agents among pregnant women in Karnataka region. *Adv Microbiol.* 2013;3:473-8.
6. Knottnerus BJ, Geerlings SE, Moll van Charante EP, ter Riet G. Women with symptoms of uncomplicated urinary tract infection are often willing to delay antibiotic treatment: a prospective cohort study. *BMC Fam Pract.* 2013;14:71.
7. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. *Ann Epidemiol.* 2000;10:509-15.
8. Fenwick EA, Briggs AH, Hawke CI. Management of urinary tract infection in general practice: a cost-effectiveness analysis. *Br J Gen Pract.* 2000;50:635-9.
9. Foxman B, Buxton M. Alternative approaches to conventional treatment of acute uncomplicated urinary tract infection in women. *Curr Infect Dis Rep.* 2013;15: 124-9.
10. Rosenberg MT, Witt ES, Barkin J, Miner M. A practical primary care approach to overactive bladder. *Can J Urol.* 2014;21 Suppl 2:2-11.
11. Homma Y, Yoshida M, Seki N, et al. Symptom assessment tool for overactive bladder syndrome-overactive bladder symptom score. *Urology.* 2006;68:318-23.
12. Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. *Eur Urol.* 2006;49:1079-86.
13. Knottnerus BJ, Bindels PJ, Geerlings SE, Moll van Charante EP, ter Riet G. Optimizing the diagnostic work-up of acute uncomplicated urinary tract infections. *BMC Fam Pract.* 2008;9:64.

14. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. *Am Fam Physician*. 2005;71:1153-62.
15. Nys S, van Merode T, Bartelds AI, Stobberingh EE. Urinary tract infections in general practice patients: diagnostic tests versus bacteriological culture. *J Antimicrob Chemother*. 2006;57:955-8.
16. Loho T, Astrawinata DAW. Bacterial and antibiotics susceptibility profile at Cipto Mangunkusumo General Hospital July-December 2014. Jakarta, Division of Infectious Diseases Department of Clinical Pathology Cipto Mangunkusumo Hospital, 2014.
17. Bollestad M, Grude N, Lindbaek M. A randomized controlled trial of a diagnostic algorithm for symptoms of uncomplicated cystitis at an out-of-hours service. *Scand J Prim Health Care*. 2015;1-8.
18. Choi H, Kim YH, Bae JH. Quality of life and changes in symptom relief in patients with acute uncomplicated cystitis treated with antibiotics: a prospective, open-label, multicenter, observational study. *Eur J Clin Microbiol Infect Dis*. 2015;34:1119-24.
19. Philips H, Huibers L, Holm Hansen E, et al. Guidelines adherence to lower urinary tract infection treatment in out-of-hours primary care in European countries. *Qual Prim Care*. 2014;22:221-31.
20. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis*. 1999;29:745-58.
21. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103-20.
22. Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs*. 2003;63:2769-802.
23. Drlica K, Hiasa H, Kerns R, Malik M, Mustaev A, Zhao X. Quinolones: action and resistance updated. *Curr Top Med Chem*. 2009;9:981-98.
24. Sorrentino F, Cartwright R, Digesu GA, Tolton L, Franklin L, Singh A, Greco P, Khullar V. Associations between individual lower urinary tract symptoms and bacteriuria in random urine samples in women. *Neurourol Urodyn*. 2015;34:429-33.
25. Patra PB, Patra S. Research findings on overactive bladder. *Curr Urol*. 2014;8:1-21.
26. Pan F, Liu D, Han XM, Li WC, Pang ZL, Li B, Zhang XP, Xiao YJ, Zeng FQ. Urodynamic investigation of cyclophosphamide-induced overactive bladder in conscious rats. *Chin Med J (Engl)*. 2012;125:321-5.
27. Su X, Nickles A, Nelson DE. Neuromodulation attenuates bladder hyperactivity in a rat cystitis model. *BMC Urol*. 2013;13:70.
28. Kageyama A, Fujino T, Taki Y, Kato Y, Nozawa Y, Ito Y, Yamada S. Alteration of muscarinic and purinergic receptors in urinary bladder of rats with cyclophosphamide-induced interstitial cystitis. *Neurosci Lett*. 2008;436:81-4.
29. Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. *BJU Int*. 2007;100:987-1006.
30. Andersson KE. Storage and voiding symptoms: pathophysiologic aspects. *Urology*. 2003;62:3-10.
31. Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. *Eur Urol*. 2012;62:1040-60.
32. Luo D, Liu L, Han P, Wei Q, Shen H. Solifenacin for overactive bladder: a systematic review and meta-analysis. *Int Urogynecol J*. 2012;23:983-91.
33. Baerheim A. Empirical treatment of uncomplicated cystitis. *Scand J Prim Health Care*. 2012;30:1-2.
34. Bleidorn J, Gagyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection?--results of a randomized controlled pilot trial. *BMC Med*. 2010;8:30.
35. Milo G, Katchman EA, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev*: CD004682, 2005.
36. Hsiao SM, Liao CH, Lin HH, Kuo HC. Duration of antimuscarinic administration for treatment of overactive bladder before which one can assess efficacy: An analysis of predictive factors. *Int Neurourol J*. 2015;19:171-7.