Long-Term Antibiotics and Novel Delivery Mechanisms for Treating Chronic Lower Urinary Tract Symptoms: A Systematic Review

Yasir Bukhari, MBBS, FRCSC[1], Ryan Chow[2], Nucelio Lemos, MD, PhD[1]

1 Department of Obstetrics and Gynaecology, University of Toronto, Toronto, ON

2 Faculty of Medicine, University of Ottawa, Ottawa, Canada

INTRODUCTION

Chronic lower urinary tract symptoms (LUTS) are a common and diverse entity. The infectious/inflammatory etiologies of LUTS have gained attention for their potential use of long-term antibiotics in treating chronic LUTS. In the infectious/inflammatory etiologies, three main diagnoses predominate: recurrent urinary tract infections (rUTI), chronic recalcitrant cystitis (CRC), and interstitial cystitis (IC). Recently, the use of long-term antibiotics has been showing promising results as a new modality to manage the infectious/inflammatory category of LUTS.

OBJECTIVE

This systematic review aims to review the literature on long-term antibiotic regimens for the treatment of chronic LUTS caused by recurrent urinary tract infections (rUTI), chronic recalcitrant cystitis (CRC), or interstitial cystitis (IC). In addition, we sought to identify novel antibiotic delivery mechanisms that may improve the treatment of chronic LUTS.

METHODS

A comprehensive search using a validated search strategy was performed on electronic databases including MEDLINE, EMBASE, Web of Science, and Clinicaltrials.gov, from their inception until March 22nd, 2022. Search terms included, but were not limited to cystitis, urogenital, antibiotic, infection, and bladder.

Inclusion criteria involved any study that evaluated the use of antibiotics for the long-term treatment (>28 days), for the treatment of chronic LUTS secondary to rUTI, CRC, or IC. Studies were also included if they examined the use of a novel antibiotic or delivery mechanism for any form of Chronic LUTS. Only studies that included primary data were included.

Screening was performed by two independent reviewers and data extraction, which encompassed key findings and quality assessment, was carried out in duplicate and independently.

RESULTS

- The systematic electronic search yielded 19,499 studies, of which only 9 studies met the eligibility criteria
- 6 RCTs, 1 observational study, and 2 basic science studies
- Studies were of a low-quality rating, with 2 of 5 studies exhibiting a high risk of bias
- Long-term, low-dose, daily antibiotic use may reduce the incidence of LUTS due to rUTI and CRC. However, the continuous use of antibiotics was associated with a higher incidence of gastrointestinal events
- First-generation cephalosporin and intermittent antimicrobial susceptibility testing may mitigate the risks of long-term antibiotics
- Multiple antibiotics regimens, as well as single antibiotic regimens, have been shown to be effective in the management of LUTS due to rUTI and CRC
- Long-term fluoroquinolones were shown to be well-tolerated and effective option
- Nitrofurantoin showed to be very effective in acute settings, although it may confer a higher-risk of adverse events with long-term us
- Evidence supporting the use of long-term antibiotics for IC was not as robust.
- Two promising novel approaches for managing LUTS: a novel delivery mechanism for Nitrofurantoin, and another that used a novel strategy to inhibit E. coli fimbriae adhesion

Author (Year)	Study Design	Control (n)	Experimental (n)	Antibiotic Used	Main Findings
Costantini et al. (2014)	Randomized Controlled Trial	67	57	Prulifloxacin; fosfomycin	No significant differences were found between the two therapy groups, in the reduction of UTI episodes during and after prophylaxis
Lau et al. (2020)	Laboratory	n/a	n/a	Nitrofurantoin in nanoparticles	The Particles were effective against a number of UTI-relevant bacterial strains
Maredia et al. (2021)	Randomized Controlled Trial	54	167	Nitrofurantoin	Breakthrough UTI developed in 88 (40%) patients on prolonged NF therapy
Rudenko & Dorofeyev (2005)	Randomized Controlled Trial	144	158	Fosfomycin trometamo	0.14 infections/patient-year in fosfomycin group and of 2.97 infections/patient-year in the placebo group
Swamy et al. (2018)	Single-arm observational Study	n/a	624	Cefalexin, nitrofurantoin, trimethoprim and more unreported	Patients on antibiotics had symptom regression and a reduction in urinary tract inflammation
Totsika et al. (2013)	Laboratory	n/a	n/a	Type 1 fimbriae adhesin inhibitor	FimH inhibitors may treat multidrug-resistant E. coli.
Warren et al. (2000)	Randomized Controlled Trial	25	25	Rifampin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin, and ciprofloxacin	Intent to treat analysis demonstrated that 12 of 25 patients in the antibiotic group reported improvement compared with 6 of 25 in the placebo group
Zhong et al. (2011)	Randomized Controlled Trial	37	31	Furantoin; sulphamethazine–trimethoprim; norfloxacin; ciprofloxacin; amoxicillin; cefaclor; or cefuroxime	Patient-initiated single-dose intermittent antibiotic prophylaxis was as effective as low-dose daily antibiotic prophylaxis in the treatment of recurrent UTIs
Elliot et al. (2016)	Randomized Controlled Trial	12	12	Gentamicin	Not completed at the time of this study

CONCLUSIONS

The evidence supporting long-term antibiotics for managing chronic LUTS is currently limited and of low quality. High-quality research is necessary to determine the optimal long-term antibiotic regimen, and there is a need for the development of novel therapies that can treat chronic LUTS without the side-effects of long-term antibiotics.

REFERENCES

- Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, Chapple CR, Kaplan S, Tubaro A, Aiyer LP, Wein AJ. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU international. 2009 Aug;104(3):352-60.
- Bilgic D, Beji NK. Lower urinary tract symptoms in women and quality of life. International Journal of Urological Nursing. 2010 Nov;4(3):97-105.
- Cox L, Rovner ES. Lower urinary tract symptoms in women: epidemiology, diagnosis, and management. Current Opinion in Urology. 2016 Jul 1;26(4):328-33.
- Swamy S, Kupelian AS, Khasriya R, Dharmasena D, Toteva H, Dehpour T, Collins L, Rohn JL, Malone-Lee J. Cross-over data supporting long-term antibiotic treatment in patients with painful lower urinary tract symptoms, pyuria and negative urinalysis. Int Urogynecol J. 2019 Mar;30(3):409-414. doi: 10.1007/s00192-018-3846-5
- Swamy S, Barcella W, De Iorio M, Gill K, Khasriya R, Kupelian AS, Rohn JL, Malone-Lee J. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: What should we do? Int Urogynecol J. 2018 Jul;29(7):1035-1043.
- Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ, Hickling D, Kapoor A, Kenton KS, Kaufman MR, Rondanina MA, Stapleton A, Stothers L, Chai TC. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol. 2019 Aug;202(2):282-289