

REVIEW

A non-pharmacological approach to the treatment of urinary tract infections: case reports with Utipro® Plus

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Abstract

Recurrent urinary tract infections (UTIs) can profoundly impair patients' quality of life and carry a substantial health resource burden. Although antibiotics are the mainstay of treatment, interest is growing in identifying antibiotic-sparing alternatives. Utipro® Plus is a medical device that acts as a mechanical barrier to protect the intestinal lumen against the adherence and invasion of uropathogenic strains of *Escherichia coli*. It is intended for the control and prevention of UTIs caused by *E. coli* and other Gram-negative uropathogens. Using illustrative case reports, this review documents outcomes

in three women with recurrent UTIs who were treated with Utipro® Plus in clinical practice.

Keywords: antimicrobial resistance, antimicrobial stewardship, quality of life, recurrent urinary tract infections, Utipro® Plus.

Citation

Cai T, Konstantinidis C, Ward S. A non-pharmacological approach to the treatment of urinary tract infections: case reports with Utipro® Plus. *Drugs in Context* 2021; 10: 2021-2-2. DOI: [10.7573/dic.2021-2-2](https://doi.org/10.7573/dic.2021-2-2)

Introduction

Urinary tract infections (UTIs) are amongst the most common infections encountered in daily clinical practice^{1,2} and range in severity from asymptomatic bacteriuria through to urosepsis.³ The majority of community-acquired uncomplicated UTIs are caused by Gram-negative bacteria of faecal flora from the *Enterobacteriaceae* family, mainly *Escherichia coli*.⁴

Due to anatomical differences, UTIs are much more frequent in women than in men.^{1,4} Urogenital manipulation, especially sexual activity, can facilitate the migration of bacteria from the vaginal cavity and rectal opening into the urethra.^{1,4} Although most UTIs are mild and self-limiting, any prior UTI is a risk factor for recurrent UTIs.⁵ Recurrent UTIs are a costly burden to healthcare systems and can have a profoundly detrimental effect on patients' quality of life.^{1,2}

Antibiotics are the mainstay of treatment for UTIs. However, resistance to Gram-negative uropathogens, including *E. coli*, is an increasing concern.⁶ The need for effective symptom relief and a reduced risk of recurrence must be balanced against the need for judicious use of antibiotics to stem the rising tide of resistance. Despite European recommendations to treat asymptomatic bacteriuria only in cases of proven benefit,³ many such patients continue to receive antibiotics

for recurring episodes, further contributing to antibiotic resistance.⁷ Identifying novel non-antibiotic approaches to UTI management is central to antibiotic stewardship.

Antibiotic-sparing strategies to prevent recurrent UTIs include, amongst others, cranberry products, probiotics, D-mannose, oestrogen and immunotherapy, although none has shown conclusive evidence that it can replace antibiotics.^{8,9} Utipro® Plus (Noventure SL, Barcelona, Spain; Monurelle Plus in Italy) is a non-pharmacological medical device intended for the control and prevention of UTIs caused by *E. coli* and other Gram-negative uropathogens. Utipro® Plus contains xyloglucan (soluble hemicellulose) and gelatin as the main components, together with propolis and extracts of *Hibiscus sabdariffa*. When combined with gelatin, xyloglucan forms a biopolymer that acts mechanically in the intestine to prevent bacteria from adhering to the mucosa,¹⁰⁻¹³ which is the first step in limiting their proliferation and migration to the urinary tract. Utipro® Plus also acts to control bacterial growth by acidifying urine pH (hibiscus and propolis) and reduces local urinary symptoms related to inflammation of the bladder mucosa.^{11,12}

Utipro® Plus is taken orally at symptom onset to reduce pathogen proliferation and can also be used prophylactically to prevent new episodes in patients with recurrent UTIs. A prospective observational study involving 67 women with

recurrent UTIs showed that prophylactic Utipro® Plus for 6 months (one capsule daily for 15 days per month) significantly reduced symptomatic recurrences and antibiotic use and improved quality of life.¹⁴

Featuring case reports from daily clinical practice, this review documents the progress of three women who were treated with Utipro® Plus for recurrent UTIs. The cases illustrate some of the clinical scenarios where Utipro® Plus can play a valuable role in antibiotic stewardship.

Patient consent

All data presented in this article are de-identified. Patient consent was not required.

Case studies

Case 1: Avoiding antibiotic resistance in UTIs with Utipro® Plus

The case involves an 85-year-old woman (non-smoker, non-drinker) with a medical history of hypertension, hyperuricemia and functional digestive syndrome, treated with enalapril, allopurinol and omeprazole, respectively.

At presentation to the Uroequip clinic in August 2015, the patient complained of dysuria, severe pollakiuria (every 30 min) and severe nocturia (more than 10 times per night). She reported considerable disruption to her regular activities and felt forced to stay at home. Her symptoms improved with antibiotic treatment, although they returned within a few days. Further questioning revealed a long history of irritative urine syndrome.

Previous ultrasound and urinary computed tomography scans were unremarkable for anatomical or functional abnormalities. Urodynamic study indicated no evidence of voiding dysfunction, hypersensitive bladder or detrusor hyperactivity. At the time of initial consult, the patient had suffered about 15 UTIs requiring antibiotic treatment in the previous 8 months, whilst concurrently receiving high doses of cranberry products plus D-mannose. Urine culture showed the presence of multiresistant extended-spectrum β -lactamase (ESBL)-producing *E. coli* sensitive to fosfomycin and carbapenems only (Table 1).

Physical examination revealed no external alterations, only mildly atrophic vaginal mucosa, which was treated with local oestrogens.

The diagnosis was recurrent multiresistant UTI.

In March 2016, an inactivated sublingual self-bacteria-based formulation was prescribed for 3 months. During that time, the patient required two fosfomycin self-treatments due to urinary symptoms. Urine culture in July 2016 showed multiresistant ESBL *E. coli* sensitive to fosfomycin and carbapenems only (Table 1).

Following another ESBL-*E. coli* recurrent multiresistant UTI, which was treated with intravenous ertapenem for 10 days in a

day-hospital setting, a new preventive strategy was introduced in October 2016 consisting of Utipro® Plus once daily for 15 days each month; 3 months later (January 2017), the patient experienced a UTI due to multisensitive *Proteus vulgaris*, which responded well to ciprofloxacin (Table 1).

Over the next 2 years, the patient experienced between one and three UTIs per year due to multisensitive bacteria, which were easily treatable with oral antibiotics according to antibiograms (Table 1). Symptoms associated with more recent UTIs were fewer and less severe than those experienced previously, thus allowing the patient to continue with her normal activities during treatment.

At the time of this report, the patient continued to receive Utipro® Plus. She still experiences about one to three multisensitive UTIs per year that are managed easily by her general practitioner and without compromise to her daily routine. She has not reported any adverse events with Utipro® Plus.

Case 2: Managing recurrent UTI with Utipro® Plus

Case 2 involves a 54-year-old woman (BMI 24 kg/m²; non-smoker, social drinker) with a medical history of hypercholesterolaemia treated with simvastatin 20 mg. There was no oncologic burden within her family. Her father died from prostate cancer.

The patient presented to the Clinic Saint Jean in November 2018 with urinary symptoms. Two days previously, she had pain onset in the lower abdomen and suprapubic region and a burning sensation whilst voiding. She described a higher-than-normal voiding frequency, including having to wake up at night, and bad-smelling urine. Symptoms had started slowly but intensified to the point where she could no longer work. Voiding alleviated the pain temporarily. On the day of the consult (third day of symptoms), she had increased her fluid intake and took paracetamol and ibuprofen but with minimal relief. She was afebrile although reported feeling unwell. Her situation was untenable for her as similar episodes were occurring every 1.5–2 months. She had been prescribed antibiotics on several occasions but invariably developed a yeast infection and an increase in vaginal pain. Mood changes and a decrease in sexual desire during the infectious episodes were creating tension in her relationship.

At presentation, her vital signs were normal: temperature 36.8°C, pulse 80 bpm, respiratory frequency normal and blood pressure 120/75 mmHg. She had suprapubic pain but no rebound tenderness. The diagnosis was acute UTI.

The patient was advised to implement lifestyle and personal hygiene changes such as increasing fluid intake and voiding after sexual intercourse. She was counselled about antibiotic use and antibiotic resistance. In the setting of an acute UTI, antibiotic treatment was deemed necessary to relieve symptoms. Targeted antibiotic treatment was possible based on urine samples.

Table 1. History of urinary tract infections (UTI) over a 5-year period in an elderly woman. A preventive strategy introduced in October 2016 consisting of Utipro® Plus once daily for 15 days each month reduced UTI frequency and changed the bacterial profile from persistently multiresistant *E. coli* to multisensitive *E. coli* (or other pathogens).

| Date | Bacteria | Extended-spectrum β -lactamase | Sensitive | Resistant |
|------------|------------------------------|--------------------------------------|--|---|
| 11/08/2015 | <i>Escherichia coli</i> | + | Fosfomycin, carbapenems | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, quinolones, trimethoprim |
| 08/09/2015 | <i>E. coli</i> | + | Carbapenems | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, quinolones, trimethoprim, fosfomycin |
| 26/07/2016 | <i>E. coli</i> | + | Fosfomycin, carbapenems | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, quinolones, trimethoprim |
| 27/10/2016 | <i>E. coli</i> | + | Fosfomycin, carbapenems | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, quinolones, trimethoprim |
| 11/10/2016 | Negative | | | |
| 11/01/2017 | Negative | | | |
| 27/01/2017 | <i>Proteus vulgaris</i> | – | Amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim | Ampicillin, fosfomycin |
| 20/02/2017 | Negative | | | |
| 27/06/2017 | <i>E. coli</i> | – | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim, fosfomycin | None |
| 19/07/2017 | Negative | | | |
| 02/11/2017 | <i>Klebsiella pneumoniae</i> | – | Amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim | Ampicillin, fosfomycin |
| 28/12/2017 | Negative | | | |
| 07/06/2018 | Negative | | | |
| 20/09/2018 | Negative | | | |
| 06/11/2018 | <i>K. pneumoniae</i> | – | Amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim | Ampicillin, fosfomycin |
| 01/02/2019 | Negative | | | |
| 23/05/2019 | <i>K. pneumoniae</i> | | Cephalosporins, carbapenems, quinolones, trimethoprim, fosfomycin | Amoxicillin + clavulanic acid, ampicillin |
| 22/07/2019 | <i>E. coli</i> | – | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim, fosfomycin | None |
| 15/10/2019 | <i>E. coli</i> | – | Ampicillin, amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim, fosfomycin | None |
| 13/01/2020 | <i>K. pneumoniae</i> | – | Amoxicillin + clavulanic acid, cephalosporins, carbapenems, quinolones, trimethoprim, fosfomycin | Ampicillin |
| 21/09/2020 | Negative | | | |

The urine sample showed *E. coli* resistant to fluoroquinolones (bacterial load: $>10^5$ CFU). Cefuroxime three times daily for 5 days was prescribed, with adjuvant Utipro® Plus twice daily during treatment. Itraconazole 150 mg once daily was prescribed for prevention.

Upon recovery, the patient was instructed to perform a urine test at the time of symptom onset (for 1 year) to determine whether *E. coli* was always the source of the UTI.

An ultrasound of the urinary tract was performed to exclude lithiasis.

At follow-up, insufficient numbers of bacteria (only haematopyuria) were found in about one-quarter of the urine tests she had performed. About half the episodes involved *E. coli* and the others involved *Klebsiella* species.

The patient was again instructed to perform a urine sample each time symptoms started and to begin taking Utipro® Plus twice daily. She was also provided with written prescriptions for antibiotics. In the absence of symptom resolution with Utipro® Plus after 48 hours, she was instructed to take one dose of fosfomycin. Using this approach, the patient had returned to the clinic only twice at the time of writing. On one occasion, the bacteria were resistant to fosfomycin and it was necessary to switch to a long course of cefuroxime (5 days). On the other occasion, she was prescribed a second course of fosfomycin with symptom resolution. Itraconazole was prescribed for each episode.

Case 3: The role of Utipro® Plus in antimicrobial stewardship in the urological setting: do not judge a book by its cover!

Case 3 describes a physically active 32-year-old woman (BMI 21.1 kg/m²; non-smoker), who had two deliveries, and an unremarkable medical history with no comorbidities, ongoing therapies, previous surgeries or relevant familial diseases.

The patient attended the urological department at the Santa Chiara Regional Hospital in January 2020 for a consult after having received three cycles of antibiotic treatment for the presence of *E. coli* in the urine in the absence of symptoms (i.e. asymptomatic bacteriuria).

In August 2019, the patient had undergone urinalysis and culture as part of an annual routine workplace screening programme and *E. coli* was isolated (bacterial load: 10^5 CFU). The antibiogram indicated susceptibility to all tested antimicrobials (no resistance). Ciprofloxacin 500 mg twice daily for 5 days was prescribed.

Seven days after the end of the first cycle of ciprofloxacin, a control urine culture revealed the presence of *E. coli* (bacterial load: 10^5 CFU) resistant to ciprofloxacin and levofloxacin. Amoxicillin plus clavulanic acid 1000 mg twice daily for 10 days was prescribed.

Three days after the end of the second cycle of amoxicillin plus clavulanic acid, a urine culture identified the presence of

E. coli (bacterial load: 10^5 CFU) resistant to fluoroquinolones, co-trimoxazole and cephalosporins.

In December 2019, the patient consulted a urologist who ordered a urinary tract ultrasound and a new urine culture. Sonography revealed no significant anatomical or functional cause for the recurring infections. Urinary culture identified *E. coli* (bacterial load: 10^5 CFU) resistant to fluoroquinolones, co-trimoxazole and cephalosporins. Gentamicin 160 mg/day for 7 days was prescribed in combination with fosfomycin 3 g/day for 4 days.

The patient continued to be asymptomatic. At the end of December 2019, another urine culture isolated *E. coli* (bacterial load: 10^5 CFU) resistant to fluoroquinolones, co-trimoxazole and cephalosporins. Soon after, she reported a vaginal discharge that required treatment with fluconazole for fungal infection.

This otherwise healthy woman was diagnosed with asymptomatic bacteriuria.

In accordance with European Association of Urology guidelines recommending against antibiotic treatment of asymptomatic bacteriuria,³ the patient was counselled about the correct approach to managing her condition and the risks associated with treating asymptomatic bacteriuria in the absence of a medical indication. The contribution of antimicrobial treatment of asymptomatic bacteriuria to increasing bacterial resistance was emphasized. A preventive approach to managing asymptomatic bacteriuria which involved taking Utipro® Plus twice daily (morning and evening) for 15 consecutive days per month, for 6 months, was suggested; the patient agreed to the new approach and was pleased to not have antibiotics prescribed.

At her next visit, the patient reported feeling well. She had not experienced any symptomatic recurrences of UTI and expressed satisfaction with the new therapeutic approach.

In a subsequent urine culture, *Enterococcus faecalis* (asymptomatic bacteriuria) was isolated but no pathogenic *E. coli* was found.

Discussion

The spread of multidrug-resistant microorganisms is increasing dramatically and requires thorough monitoring and novel preventive approaches.¹⁵ Improper antibiotic use and antimicrobial resistance have become significant issues worldwide.¹⁵ Over the past few years, there has been growing interest and research into the non-antibiotic prophylaxis of UTIs. In particular, the use of phytotherapy and nutraceuticals has been proposed as a feasible and effective alternative approach to curtail the use of antibiotics and the rate of symptomatic recurrences.⁸

Utipro® Plus offers a novel approach to the management of UTIs. In addition to the protective barrier effect of xyloglucan-gelatin on mucosal epithelial cells,^{10,11} hibiscus and propolis may have bacterial anti-adhesive effects at the urinary level.^{16,17} The medical device is devoid of any antibacterial activity¹¹ and may have

specificity for faecal *E. coli* and *Enterococcus* spp.¹² Clinically, Utipro® Plus is intended to control symptomatic UTIs and to prevent symptomatic recurrences, as illustrated in the case studies.

Case 1 had several well-established risk factors for UTIs, including advanced age, female gender and, most notably, a long history of previous UTIs. Symptom frequency and severity had profoundly impaired her quality of life. Prophylactic use of Utipro® Plus led to a decrease in UTI frequency from 15 episodes per year to 1–3 episodes per year, greatly alleviating the disease burden and reducing antibiotic use. Importantly, during treatment with Utipro® Plus, the patient's UTI bacterial profile changed from persistently multiresistant *E. coli* to multisensitive *E. coli* (or other pathogens) that were easily treatable with oral antibiotics. The conversion from multidrug-resistant to drug-sensitive strains is likely due to reduced antibiotic exposure and thus to the forces of selective pressure, which are specific for the type of antibiotic and bacterial species. The patient was able to return to her regular activities and recovered her quality of life. She reported no adverse effects with Utipro® Plus. In this patient, Utipro® Plus provided an effective and sustained reduction of UTI recurrences and was safe to use despite her advanced age and comorbidities.

Case 2 derived considerable benefit from a change in approach to using Utipro® Plus as an adjuvant to antibiotic treatment for symptomatic UTIs. The number of clinic visits due to recurrent UTIs, antibiotic-induced yeast infections, and pain decreased from around 10 per year prior to the use of Utipro® Plus to two in 2019. The associated decrease in antibiotic usage resulted in fewer yeast infections. In this patient, the use of Utipro® Plus led to considerable improvements in her quality of life (ability to go to work) and sexual health.

Case 3 demonstrated that the use of Utipro® Plus in a patient experiencing multiple recurrent uncomplicated UTIs led to fewer recurrences and minimized antibiotic use. The patient was compliant with the product, experienced no adverse effects and reported an improvement in her quality of life. Importantly, from a microbiological point of view, a transition from symptomatic UTI to asymptomatic bacteriuria was observed.

Current opinion is that asymptomatic bacteriuria plays a protective role in preventing symptomatic recurrences of UTI

by inhibiting the colonization of enteric pathogens such as *E. coli*. European Association of Urology guidelines state that the 'treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections' (level of evidence: 1B; strength of recommendation: strong).³ Importantly, asymptomatic bacteriuria is not a recurrence. Recent data regarding patient-related and pathogen-related factors influencing recurrent UTIs suggest that effective management is likely to require the consideration of bacterial reservoirs at anatomical sites other than the urinary tract. In a randomized clinical trial of 673 consecutive women with asymptomatic bacteriuria affected by recurrent UTIs, after 12 months' follow-up, the rate of symptomatic UTIs was significantly higher in subjects who were treated *versus* not treated with antibiotics (46.8 *versus* 13.1%; $p < 0.001$).¹⁸ In women affected by recurrent UTIs, asymptomatic bacteriuria due to *E. faecalis* appears to be an important defence mechanism that effectively interferes with the establishment of many important enteric pathogens, such as *E. coli*, thus reducing the rate of symptomatic recurrences.¹⁸ In this respect, the use of an antibiotic-sparing approach should be preferred as it does not alter the typical intestinal microbiota. The observation that Utipro® Plus was able to establish asymptomatic bacteriuria in Case 3 is evidence of its lack of effect on normal microbiota.

Conclusions

Reducing the severity and frequency of symptomatic UTIs is associated with improvements in quality of life and cost savings to society due to fewer physician visits. An antibiotic-sparing strategy in persons affected by recurrent UTIs is a useful means of preserving the quality of antimicrobial stewardship in preventing microbial resistance. As illustrated by these case reports of women with recurrent UTIs, Utipro® Plus appears to have an important and valuable role in everyday clinical practice as a non-antimicrobial option to control and prevent UTIs. With respect to its place in therapy, Utipro® Plus will not entirely replace antibiotics in patients with recurrent UTIs but is an additional tool that can be used to achieve successful outcomes and limit antibiotic use. Access to Utipro® Plus is easy as it is available over the counter and can be ordered online.

Contributions: The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: TC has received travelling and speaking grants from Noventure. CKG has served as a freelance medical advisor for pharmaceutical and biotech companies including Devicare, Ferrer and Noventure. SW has served as a consultant for Goodlife (propiverine) and Merck (Cran Fyt Plus). The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: <https://www.drugsincontext.com/wp-content/uploads/2021/05/dic.2021-2-2-COI.pdf>

Acknowledgements: Medical writing assistance was provided by Kerry Dechant of behalf of Content Ed Net (Madrid, Spain), with funding by Noventure SL, Barcelona, Spain. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

Funding declaration: Writing assistance was funded by Noventure SL, Barcelona, Spain.

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Article URL: <https://www.drugsincontext.com/a-non-pharmacological-approach-to-the-treatment-of-urinary-tract-infections--case-reports-with-utipro-plus>

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Provenance: Submitted; externally peer reviewed.

Submitted: 16 February 2021; **Accepted:** 13 April 2021; **Publication date:** 24 May 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

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