CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Non-antimicrobial therapies for recurrent urinary tract infection in adults: is there a place for faecal microbiota transplantation?

Journal:	*Clinical Microbiology and Infection*
Manuscript ID	CLM-24-29373.R1
Article Type:	Narrative Review
Date Submitted by the Author:	20-May-2025
Complete List of Authors:	Cassir, Nadim ; Institut Hospitalier Universitaire - Méditerranée Infection., Unité de Recherche sur les Maladies Infectieuses Tropicales et Emergentes Ghani, Rohma; Imperial College London Faculty of Medicine, Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, Biehl , Lena ; University Hospital of Cologne, Department I of Internal Medicine; German Centre for Infection Research, partner site Bonn-Cologne Graells, Tiscar; Karolinska Institutet, Huddinge, Stockholm, Sweden, Department of Neurobiology, Care Sciences and Society (NVS), Division of Family Medicine and Primary Care, Kuijper, Ed; LUMC, Medical Microbiology Mullish, Benjamin; Imperial College Faculty of Medicine, Division of Integrative Systems Medicine and Digestive Disease Marchesi, Julian; Imperial College Faculty of Medicine, Division of Integrative Systems Medicine and Digestive Disease; Cardiff University, School of Biosciences BENECH, Nicolas ; Hospices Civils de Lyon, Infectious Disease
Key Words:	Urinary tract infection, faecal microbiota transplantation, gut microbiota, multidrug resistant organisms, urinary microbiome

Abstract:	Background: Recurrent urinary tract infection (rUTI) is a common condition, affecting approximately one-third of women after an initial UTI. It significantly impacts healthcare costs and patient quality of life. The relationship between the pathophysiology of UTI and the gut and vaginal microbiota is recognised as a contributing factor to rUTI in women. As antibiotic resistance among uropathogens continues to increase, there is a clear need to develop novel therapeutic interventions. Faecal microbiota transfer (FMT) is a potent non-antimicrobial strategy for modulating the gut microbiota; however, its clinical relevance in the context of rUTI is unclear. Objectives: This narrative review aims to summarise the current evidence on the use of FMT for the treatment of rUTI in women, excluding those with mechanical dysfunctions such as urinary incontinence, neurogenic bladder, and bladder cancer, compared with other non-antimicrobial interventions. We also discuss the pathophysiology and epidemiology of

	rUTI to identify patients for whom microbiota-targeted therapies may be the most effective. Content: Periurethral colonization and migration to the bladder of uropathogens that inhabit the gut and vagina has been linked to the aetiology of UTI in women, particularly in patients with multidrug resistant organisms (MDRO). FMT appears to be a promising approach for preventing the clinical development of rUTI, although prospective data remain limited. In contrast, other reported non-antimicrobial strategies targeting the gut and urogenital microbiota have shown variable significant clinical efficacy. Prospective randomised controlled clinical trials are then needed to further confirm a potential therapeutic benefit, optimise the FMT procedure and better assess its cost-effectiveness.

SCHOLARONE™
Manuscripts

Non-antimicrobial therapies for recurrent urinary tract infection in women: is there a place for faecal microbiota transfer?

Nadim CASSIR[1,2§*], Rohma GHANI[3§], Lena M. BIEHL[4,5], Tiscar GRAELLS[6], Ed J KUIJPER[7], Benjamin H. MULLISH[3,8], Julian R. MARCHESI[3], Nicolas BENECH[9*]

On behalf of the ESGHAMI group

§ contributed equally to this work

* Corresponding authors

[1] Aix Marseille Univ, APHM (Infectious Diseases), MEPHI, Marseille, France.

[2] IHU-Méditerranée Infection, Marseille, France.

[3] Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, UK.

[4] Department of Internal Medicine, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany

[5] German Centre of Infection Research (partner site Bonn-Cologne), Cologne, Germany.

[6] Department of Neurobiology, Care Sciences and Society (NVS), Division of Family Medicine and Primary Care, Karolinska Institutet, Huddinge, Stockholm, Sweden.

[7] Center for Microbiota Analysis and Therapeutics, Leiden University Center for Infectious Diseases (LUCID), Leiden University Medical Center (LUMC), Leiden, The Netherlands.

[8] Departments of Gastroenterology and Hepatology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

[9] Hepato-Gastroenterology Department, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France.

For Peer Review

Epidemiology of recurrent urinary tract infections (rUTIs)

Urinary tract infections (UTIs) are the inflammatory response of the urothelium to microbial pathogens (1). They are among the most common bacterial infections that are encountered in clinical settings and have increased over the last three decades to over 400 million cases per year worldwide (2). Recurrent UTIs (rUTIs) are typically defined as at least 2 culture-proven episodes in 6 months, or at least 3 in one year (3). Approximately 20 to 30% of women who have a first UTI will have rUTI (4,5). Since the majority of rUTI patients are women, we will focus on this patient group in our review. Patients with urological dysfunction such as urinary incontinence, neurogenic bladder, and bladder cancer are beyond the scope of this narrative review.

Appropriate diagnosis of UTIs, a disease that imposes a significant burden on individual patients and society as a whole, is hampered by several factors such as the lack of clear diagnostic tests beyond urine culture and microscopy results, the non-specific signs and symptoms of patients, particularly those in nursing homes, the disparity between asymptomatic bacteriuria and clinical infection, the high rates of contamination during urine collection, and finally variable knowledge of appropriate indications for ordering urine cultures. These important gaps have been addressed in a recent consensus-based reference standard for UTI, with the potential to improve both the internal and external validity of future UTI studies (6). Recurrent UTIs have a significant negative impact on patients' health-related quality of life (7,8). In addition, rUTI are associated with an economic burden on the individual (9), and on the use of healthcare resources (10).

Recurrent UTIs also have a specific impact on kidney transplant patients, leading to poorer graft function and reduced survival compared to patients with no UTIs or only a single UTI (11,12). Interactions with immunosuppressants and effects on renal function may also affect anti-microbial options particularly in cases of drug-resistant infections (3).

For Peer Review

Treatment options for rUTI

Antibiotics are the main treatment for UTIs and rUTIs. Remarkably, almost 25% of all human antibiotic prescriptions are for UTIs (13). However, the impact of recurrent courses of antibiotics is far-reaching (5). One well-recognised consequence of repeated antibiotic use is the development, selection and spread of multidrug-resistant organisms (MDROs) (14). MDROs are defined as organisms that are not susceptible to at least one antimicrobial in three or more classes, based on *in vitro* antibiotic susceptibility testing (15). MDRO infections lead to poorer outcomes, in part due to inappropriate empiric therapy, resulting in increased treatment failures and readmissions for the same infection, as well as an increased burden of healthcare costs (16). MDROs are more likely to colonise the gut microbiota following antibiotic use (17,18) as this directly reduces antibiotic-susceptible commensals (19). In addition, the loss of bacterial diversity in the gut consecutive to antibiotic exposure reduces the ability of the gut microbiota to prevent infection and pathogen colonisation (20). In addition to repeated exposure to antibiotic treatments, patients with rUTIs are often prescribed long-term prophylactic antibiotics, with combined ecological and toxicity issues.

In the context of a global initiative to reduce the use of antimicrobials (21), non-antimicrobial therapies for the prevention of rUTIs have been trailed with variable success (13). The most widely used ones in clinical practice are detailed in **Table 1**. To date, long-term outcome data are limited and there is not a one size fits all' regimen (22).

The Urinary Microbiome

The urinary microbiome refers to the community of microorganisms — including bacteria, viruses, fungi, and other microbes — that inhabit naturally the urinary tract. The urinary microbiome in women is complex, variable, and still understudied. It is still not possible to define a healthy urinary microbiome. Due to the limitations of standard bacterial culture methods and the fact that bacterial counts below 10^3 CFU/mL are considered 'negative', it has

For Peer Review

long been believed that the bladder is sterile (considering culturable microorganisms) in the absence of infection (34). However, due to recent advances in gene sequencing, we now know that the urinary tract (*i.e.,* urethra, bladder, and kidney) has its own microbiome (35). A recent study of the human urinary tract bacterial repertoire identified 562 different bacterial species, referred to as part of the urinary microbiome (36). Women with rUTIs have been shown to have a different urinary microbiome composition than controls (37,38) (Figure 1). However, we don't know whether this distinctive urinary microbiome preceded the UTI as a risk factor or was a consequence of having the UTI, as we don't have prospective studies/data on the pre-UTI microbiome. Local determinants of the urinary ecological niche that are known risk factors for rUTI include the decrease of oestrogen levels in women which is linked to a reduction in *lactobacilli* in the urinary microbiome (39) and, indeed, menopause makes women more susceptible to developing rUTI. In addition, it has been shown that the urinary microbiome of women with rUTI was enriched for antimicrobial resistance genes (ARGs), regardless of their current UTI status (39). Furthermore, women with rUTI can develop persistent intracellular bacterial colonies (IBC) in their bladder urothelium which may serve as a reservoir for recurrent episodes (40) (Figure 2).

Gut-vagina-bladder axis

The relationship between the pathophysiology of UTI in women and the gut and vaginal microbiota is being recognised as a contributing factor to rUTI (41). Periurethral colonization and migration to the bladder of uropathogens colonising the gut and vagina has been identified as a causative factor in the aetiology of UTI (42–44). In women, the vaginal microbiota appears to play a critical role in inhibiting pathogen colonisation, growth and transition to the periurethral area and bladder. Following vaginal microbiota perturbation, a reduced abundance of *Lactobacillus* and an increase relative abundance of other potential pathogens such as *Escherichia coli* are recognised to favour UTI (45). Recent studies suggest that the presence of

For Peer Review

certain virulence factors adhesion genes, fimbria genes, flagellin genes, capsular genes, motility genes, iron uptake gene, toxin genes and two-component response system genes together with resistance profiles of uropathogenic *Escherichia coli* (can predict the likelihood of a patient developing a UTI (46). Metabolic activity of the gut microbiota may also be associated with the risk of UTI. Indeed, Worby *et al.* showed that patients with recurrent UTI had significantly lower levels of butyrate-producing bacteria and reduced gut microbial richness compared with controls, and that antibiotic treatment failed to eradicate uropathogens from the gut microbiota (47). Moreover, Magruder *et al.* showed that high relative abundances of *Faecalibacterium* and *Romboutsia* in the gut microbiota were associated with a decrease of *Enterobacteriaceae* in urine and UTI in kidney transplant recipients, suggesting direct modulation of the urinary microbiome by the gut microbiota in this population (48). Further studies in infants reported that abnormal development of the gut microbiota during infancy increases the risk of developing febrile UTI. This was suggested by a significant difference in diversity metrics of their gut microbiota, in particular a higher proportion of *Escherichia-Shigella* (49).

Thus, based on these data, the gut microbiota appears to act as a direct modulator of potential uropathogens within the urinary microbiome, positioning it as a promising therapeutic target for the management of rUTI.

Faecal Microbiota Transplantation

Faecal microbiota transplantation (FMT) involves the transfer of screened donor stool into a recipient's gastrointestinal tract to restore gut microbiota diversity and potentially exert therapeutic effects. Stool preparations are usually administrated through gastric/duodenal infusion, enema, frozen or lyophilized capsule, or colonoscopy with very good tolerance. It is the only microbiome-based therapy that allows the transfer of an entire complex ecosystem in the gut, including bacteria, fungi, protozoa and viruses, as well as the environment in which they are found (including metabolites and other potential soluble mediators of relevance) (50).

For Peer Review

Its efficacy in the treatment of recurrent *Clostridioides difficile* infection (51), without the necessity to eradicate *C. difficile* from the intestinal tract has led to the exploration of other potential applications of this modality against other enteric pathogens (52). Although to date only results from case reports and retrospective case series are available (**Table 2:**), they indicate a trend towards a reduction in the frequency and severity of urinary tract infections following FMT for rUTI (53–55), without complete eradication of the causative microorganisms. While no randomised controlled trial has been published evaluating FMT for rUTI, there are several prospective clinical trials currently registered with results pending or recruitment underway (NCT03367910, NCT06050148, NCT03786900, NCT03050515). However, to date there is no agreed international position on how FMT should be regulated. As a result, there is likely to be significant variation in the data and approaches used to regulate FMT-based products in clinical trials and to monitor the use of FMT in clinical practice. This has implications for protecting the safety of patients receiving FMT and could also limit the availability of FMT. In the EU, the new regulation on quality and safety standards for substances of human origin intended for human application, published in 2024 (https://health.ec.europa.eu/blood-tissues-cells-and-organs/soho-regulation/new-eu-rules-substances-human-origin_en), should allow for better harmonisation of practices.

Knowledge gap and research agenda

As the understanding of the role between both the genitourinary and gut microbiota on infection grows, there is an increasing interest in the use of FMT treatment for rUTIs, particularly in those patients with limited antibiotic options (due to side effects and antibiotic resistance), or those with limited responsiveness to non-antimicrobial therapies. Interventions on the vaginal microbiome are also of interest for prevention of rUTI in women but are currently mainly studied for the treatment and prevention of chronic vaginosis. This review demonstrates

For Peer Review

that there are research gaps to be addressed before FMT treatment for rUTI can be widely utilised **(Figure 3)**.

From a clinical perspective, the studies to date have been a mixture of case reports and small retrospective case series, and the outcomes of the randomised controlled trials are still awaited to evaluate the impact of selection and reporting bias in these papers. Both clinical outcome parameters and microbiological parameters should be defined in further studies. For example, in patients treated with FMT for recurrent *C. difficile* infection, it is not clear whether controlling diarrhoea and limiting the risk of recurrence *per se* has an impact on reducing the risk of rUTI. Another factor is the evaluation of how long these clinical benefits last and whether repeated transplants may be necessary. In terms of prioritization of limited resources, further studies are needed to evaluate who can benefit most from this treatment such as renal transplant recipients or those refractory to other alternative therapies. In general, the cost of FMT is likely to be higher than other therapeutic interventions, but a cost-benefit analysis (including prevention of hospital admissions) for specific patient groups has not been carried out (70,71). In addition, the protocols used to date for FMT in MDRO patients are identical to those used for rCDI patients in terms of donor selection, slurry preparation, storage and route and volume of administration. Future areas of research should include randomised trials, taking into account a better understanding of mechanisms, to identify markers of treatment success in order to better select future recipients. There are also many unanswered questions about the exact procedures for FMT: Is pre-treatment with an antibiotic necessary and, if so, should it target the last uropathogen detected? What is the optimal dosage and should the procedure be repeated (72)? Another issue that should be addressed in larger clinical trials is whether repeated FMT is necessary in patients who show a partial response.

In addition, from a mechanistic perspective, further investigation into detailed microbial dynamics and potential adverse effects is needed. This would allow a better understanding of

For Peer Review

how decolonisation of MDROs occurs with FMT (52). Furthermore, follow-up with microbiological surveillance is important to gain more insight into adverse events (73). The potentially beneficial mechanism of FMT is likely to be a multifactorial process involving the restoration of colonisation resistance and the functional properties of commensal bacteria and their metabolites - such as short-chain fatty acids and bile acids - which have a wide range of functions including the protection of gut barrier function and immunomodulatory effects (74-81). Indeed, the interplay between the gut microbiota and the immune system may modulate inflammation and the onset of symptoms and may, thus, even have an impact on rUTI in cases where the uropathogen resides in intracellular colonies in the bladder. In support of this, previous FMT studies have shown a reduction in invasive infections following the procedure (82-84).

In conclusion, rUTIs have limited therapeutic options. As a last resort when other alternatives have failed, FMT could be a potentially relevant therapy with a favourable safety profile and existing biological rationale. However, stronger clinical evidence is needed to validate existing preclinical and clinical data, and to refine potential indications and procedural details. We therefore propose a research agenda **(Figure 3)**. First, donor screening is the primary means of ensuring the safety of FMT. To date, transmission of infections through FMT has occurred because of inadequate donor screening, such as the use of microbiological tests with suboptimal test characteristics or failure to test for certain pathogens (85). However, donor screening does not include testing for the presence of uropathogenic microorganisms and testing for its capacity to eradicate these bacteria in vitro. The selection of "optimal" or "super" donors varies with the indication of interest and therefore needs to be better defined for the potential treatment of rUTIs. Secondly, the optimization, standardization, and feasibility of the different manufacturing processes and formulations for the population at risk of rUTIs needs to be better addressed. For this indication, lyophilised FMT products (which can be administered

For Peer Review

in capsular form) appear to be more appropriate. Thirdly, FMT also appears to be well tolerated in special populations, including paediatric, immunosuppressed and cirrhotic patients (85). However, the evidence for severely immunocompromised individuals remains sparse and warrant rigorous evaluation. Finally, the extent to which recipient characteristics contribute to the success of FMT for the treatment of rUTIs remains to be established. Such characteristics may relate to anatomical factors, immune parameters, dietary patterns or microbiome composition. In this context, the selection of optimal recipients remains a challenge for future studies.

For Peer Review

Figure 1: The urinary microbiome in women without urinary symptoms compared to the urinary microbiome of women with (recurrent) urinary tract infections ((r)UTI).

Created in BioRender. Graells, T. (2025) https://BioRender.com/pvb0jlo

Figure 2: Factors in pathogenesis of (recurrent) UTI in women.

Host factors include hormones and the immune system. Intestinal microbiota can act as a reservoir of pathogens or exhibit colonisation resistance. Vaginal microbiota influences the transition from the gut to the bladder. The role of urinary microbiota and intracellular bacterial colonies warrant further studies.

Created in BioRender. Biehl, L. (2025) https://BioRender.com/s92d726

Figure 3: Research agenda to optimise the use of faecal microbiota transplantation for the treatment of recurrent urinary-tract infections.

Table 1: Examples of non-antimicrobial modalities utilised to prevent recurrent urinary tract infections (rUTIs).

UPEC: uropathogenic *Escherichia coli*. RCT: randomized controlled trial.

Table 2: Recent studies on the usefulness of faecal microbiota transplantation (FMT) for treating recurrent urinary tract infections (rUTIs).

ESBL: Extended Spectrum Beta-Lactamase FMT: faecal microbiota transplantation. NG: naso-gastric, NJ: nasojejunal rCDI: recurrent *Clostridioides difficile* infection, rUTI: recurrent urinary tract infection, UTI: urinary tract infection.

* Beyond the published follow-up, the author has followed up for 36 months and no rUTI occurred.

For Peer Review

Fundings: The Division of Digestive Diseases receives financial support from the National Institute of Health Research (NIHR) Imperial Biomedical Research Centre (BRC) based at Imperial College London and Imperial College Healthcare NHS Trust. BHM is the recipient of a Medical Research Council (MRC) Clinician Scientist award (MR/Z504002/1).

Conflicts of interest: BHM has received consultancy fees from Finch Therapeutics Group and Ferring Pharmaceuticals**.** N.B. received lecture fees from Tillots Pharma and travel grants from Pfizer, participated on an adivisory board for Ferring Pharmaceuticals and Tillots Pharma with payment to his institution, is a PI of a clinical trial supported by Exeliom Biosciences. No other potential conflicts of interests were reported.

Authors contribution: All authors contributed to the of the narrative review and writing the manuscript. All authors approved the final version for publication.

For Peer Review

References

1. Stamm WE, Norrby SR. Urinary Tract Infections: Disease Panorama and Challenges. *The Journal of Infectious Diseases*. 2001;183(Supplement_1): S1–S4. https://doi.org/10.1086/318850.
2. Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi F. Disease burden and long-term trends of urinary tract infections: A worldwide report. *Frontiers in Public Health*. 2022;10. https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2022.888205
3. Brubaker L, Carberry C, Nardos R, Carter-Brooks C, Lowder JL. American Urogynecologic Society Best-Practice Statement: Recurrent Urinary Tract Infection in Adult Women. *Urogynecology*. 2018;24(5). https://journals.lww.com/fpmrs/fulltext/2018/09000/american_urogynecologic_society_best_practice.2.aspx
4. Vazquez-Montes MDLA, Fanshawe TR, Stoesser N, Walker AS, Butler C, Hayward G. Epidemiology and microbiology of recurrent UTI in women in the community in Oxfordshire, UK. *JAC-Antimicrobial Resistance*. 2024;6(1): dlad156. https://doi.org/10.1093/jacamr/dlad156.
5. Bader MS, Hawboldt J, Brooks A. Management of complicated urinary tract infections in the era of antimicrobial resistance. *Postgraduate Medicine*. 2010;122(6): 7–15. https://doi.org/10.3810/pgm.2010.11.2217.
6. Bilsen MP, Conroy SP, Schneeberger C, Platteel TN, van Nieuwkoop C, Mody L, et al. A reference standard for urinary tract infection research: a multidisciplinary Delphi consensus study. Lancet Infect Dis 2024;24:e513–21. https://doi.org/10.1016/S1473-3099(23)00778-8.
7. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-related quality of life. *BJU International*. 2012;110(11c): E830–E836. https://doi.org/https://doi.org/10.1111/j.1464-410X.2012.11337.x.
8. Renard J, Ballarini S, Mascarenhas T, Zahran M, Quimper E, Choucair J, et al. Recurrent Lower Urinary Tract Infections Have a Detrimental Effect on Patient Quality of Life: a Prospective, Observational Study. *Infectious Diseases and Therapy*. 2015;4(1): 125–135. https://doi.org/10.1007/s40121-014-0054-6.
9. Wagenlehner F, Wullt B, Ballarini S, Zingg D, Naber KG. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). *Expert Review of Pharmacoeconomics & Outcomes Research*. 2018;18(1): 107–117. https://doi.org/10.1080/14737167.2017.1359543.
10. Öztürk R, Murt A. Epidemiology of urological infections: a global burden. *World Journal of Urology*. 2020;38(11): 2669–2679. https://doi.org/10.1007/s00345-019-03071-4.
11. Britt NS, Hagopian JC, Brennan DC, Pottebaum AA, Santos CAQ, Gharabagi A, et al. Effects of recurrent urinary tract infections on graft and patient outcomes after kidney transplantation. *Nephrology Dialysis Transplantation*. 2017;32(10): 1758–1766. https://doi.org/10.1093/ndt/gfx237.
12. Al-Hasan MN, Razonable RR, Kremers WK, Baddour LM. Impact of gram-negative bloodstream infection on long-term allograft survival after kidney transplantation. *Transplantation*. 2011;91(11): 1206–1210. https://doi.org/10.1097/TP.0B013E3182180535.
13. Sihra N, Goodman A, Zakri R, Sahai A, Malde S. Nonantibiotic prevention and management of recurrent urinary tract infection. *Nature Reviews Urology*. 2018;15(12): 750–776. https://doi.org/10.1038/s41585-018-0106-x.

For Peer Review

14. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *The Lancet Planetary Health*. 2021;5(12): e893–e904. https://doi.org/10.1016/S2542-5196(21)00280-1.
15. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. 2012;18: 268–281. https://doi.org/10.1111/j.1469-0691.2011.03570.x
16. Macvane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum β-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *Journal of Hospital Medicine*. 2014;9(4): 232–238. https://doi.org/10.1002/jhm.2157.
17. Tacconelli E, De Angelis G, Cataldo MA, Mantengoli E, Spanu T, Pan A, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: A hospital population-based study. *Antimicrobial Agents and Chemotherapy*. 2009;53(10): 4264–4269. https://doi.org/10.1128/AAC.00431-09.
18. Casals-Pascual C, Vergara A, Vila J. Intestinal microbiota and antibiotic resistance: Perspectives and solutions. *Human Microbiome Journal*. 2018;9: 11–15. https://doi.org/10.1016/J.HUMIC.2018.05.002.
19. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. *Clinical Infectious Diseases*. 2012;55(7): 905–914. https://doi.org/10.1093/cid/cis580.
20. Sullivan Å. Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infectious Diseases*. 2001;1(2): 101–114. https://doi.org/10.1016/S1473-3099(01)00066-4.
21. O'Neill J. *Review on antimicrobial resistance: tackling drug-resistant infections globally: final report and recommendations*. 2016. p. 80 pp.
22. Kaußner Y, Röver C, Heinz J, Hummers E, Debray TPA, Hay AD, et al. Reducing antibiotic use in uncomplicated urinary tract infections in adult women: a systematic review and individual participant data meta-analysis. *Clinical Microbiology and Infection*. 2022;28(12): 1558–1566. https://doi.org/10.1016/j.cmi.2022.06.017.
23. Mayrer AR, Andriole VT. Urinary tract antiseptics. *The Medical clinics of North America*. 1982;66(1): 199–208. https://doi.org/10.1016/s0025-7125(16)31453-5.
24. Heltveit-Olsen SR, Sundvall PD, Gunnarsson R, Snaebjörnsson Arnljots E, Kowalczyk A, Godycki-Cwirko M, et al. Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU). *BMJ Open*. 2022;12(11): e065217. https://doi.org/10.1136/bmjopen-2022-065217.
25. Bakhit M, Krzyzaniak N, Hilder J, Clark J, Scott AM, Mar C Del. Use of methenamine hippurate to prevent urinary tract infections in community adult women: a systematic review and meta-analysis. *British Journal of General Practice*. 2021;71(708): e528. https://doi.org/10.3399/BJGP.2020.0833.
26. Aziminia N, Hadjipavlou M, Philippou Y, Pandian SS, Malde S, Hammadeh MY. Vaccines for the prevention of recurrent urinary tract infections: a systematic review. *BJU International*. 2019;123(5): 753–768. https://doi.org/https://doi.org/10.1111/bju.14606.
27. Prattley S, Geraghty R, Moore M, Somani BK. Role of Vaccines for Recurrent Urinary Tract Infections: A Systematic Review. *European Urology Focus*. 2020;6(3): 593–604. https://doi.org/https://doi.org/10.1016/j.euf.2019.11.002.

For Peer Review

28. Raz R, Colodner R, Rohana Y, Battino S, Rottensterich E, Wasser I, et al. Effectiveness of Estriol-Containing Vaginal Pessaries and Nitrofurantoin Macrocrystal Therapy in the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women. *Clinical Infectious Diseases*. 2003;36(11): 1362–1368. https://doi.org/10.1086/374341.
29. Chen YY, Su TH, Lau HH. Estrogen for the prevention of recurrent urinary tract infections in postmenopausal women: a meta-analysis of randomized controlled trials. *International Urogynecology Journal*. 2021;32(1): 17–25. https://doi.org/10.1007/s00192-020-04397-z.
30. Hayward G, Mort S, Hay AD, Moore M, Thomas NPB, Cook J, et al. d-Mannose for Prevention of Recurrent Urinary Tract Infection Among Women: A Randomized Clinical Trial. *JAMA Internal Medicine*. 2024;184(6): 619–628. https://doi.org/10.1001/jamainternmed.2024.0264.
31. Cooper TE, Teng C, Howell M, Teixeira-Pinto A, Jaure A, Wong G. D-mannose for preventing and treating urinary tract infections. *Cochrane Database of Systematic Reviews*. 2022;(8). https://doi.org/10.1002/14651858.CD013608.pub2.
32. Gupta V, Mastromarino P, Garg R. Effectiveness of Prophylactic Oral and/or Vaginal Probiotic Supplementation in the Prevention of Recurrent Urinary Tract Infections: A Randomized, Double-Blind, Placebo-Controlled Trial. *Clinical Infectious Diseases*. 2024;78(5): 1154–1161. https://doi.org/10.1093/cid/ciad766.
33. Abdullatif VA, Sur RL, Eshaghian E, Gaura KA, Goldman B, Panchatsharam PK, et al. Efficacy of Probiotics as Prophylaxis for Urinary Tract Infections in Premenopausal Women: A Systematic Review and Meta-Analysis. *Cureus*. 2021;13(10): e18843. https://doi.org/10.7759/cureus.18843.
34. Roth RS, Liden M, Huttner A. The urobiome in men and women: a clinical review. *Clinical Microbiology and Infection*. 2023;29(10): 1242–1248. https://doi.org/10.1016/j.cmi.2022.08.010.
35. E HE, Kathleen M, M PM, B RA, J ZM, R ME, et al. Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder. *Journal of Clinical Microbiology*. 2020;52(3): 871–876. https://doi.org/10.1128/jcm.02876-13.
36. Aurélie M, Florent C, Jean-Charles D, Michel T, Jean-Christophe L, Didier R. Human Bacterial Repertoire of the Urinary Tract: a Potential Paradigm Shift. *Journal of Clinical Microbiology*. 2019;57(3): 10.1128/jcm.00675-18. https://doi.org/10.1128/jcm.00675-18.
37. M PM, E HE, B RA, J ZM, Krystal TW, Cynthia F, et al. The Female Urinary Microbiome: a Comparison of Women with and without Urgency Urinary Incontinence. *mBio*. 2014;5(4): 10.1128/mbio.01283-14. https://doi.org/10.1128/mbio.01283-14.
38. Joyce C, Halverson T, Gonzalez C, Brubaker L, Wolfe AJ. The Urobiomes of Adult Women With Various Lower Urinary Tract Symptoms Status Differ: A Re-Analysis. *Frontiers in Cellular and Infection Microbiology*. 2022;12. https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2022.860408
39. Neugent ML, Kumar A, Hulyalkar N V, Lutz KC, Nguyen VH, Fuentes JL, et al. Recurrent urinary tract infection and estrogen shape the taxonomic ecology and function of the postmenopausal urogenital microbiome. *Cell Reports Medicine*. 2022;3(10). https://doi.org/10.1016/j.xcrm.2022.100753.

For Peer Review

40. Mysorekar IU, Hultgren SJ. Mechanisms of uropathogenic Escherichia coli persistence and eradication from the urinary tract. *Proceedings of the National Academy of Sciences*. 2006;103(38): 14170–14175. https://doi.org/10.1073/pnas.0602136103.
41. Robert T, A RK, Tiffany H, A WM, Bin W, J SD, et al. Comparative Genomics of Antibiotic-Resistant Uropathogens Implicates Three Routes for Recurrence of Urinary Tract Infections. *mBio*. 2019;10(4): 10.1128/mbio.01977-19. https://doi.org/10.1128/mbio.01977-19.
42. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*. 2015;13(5): 269–284. https://doi.org/10.1038/nrmicro3432.
43. Magruder M, Sholi AN, Gong C, Zhang L, Edusei E, Huang J, et al. Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection. *Nature Communications*. 2019;10(1): 5521. https://doi.org/10.1038/s41467-019-13467-w.
44. Yamamoto S, Tsukamoto T, Terai A, Kurazono H, Takeda Y, Yoshida O. Genetic Evidence Supporting the Fecal-Perineal-Urethral Hypothesis in Cystitis Caused by Escherichia Coli. *The Journal of Urology*. 1997;157(3): 1127–1129. https://doi.org/https://doi.org/10.1016/S0022-5347(01)65154-1.
45. Lewis AL, Gilbert NM. Roles of the vagina and the vaginal microbiota in urinary tract infection: evidence from clinical correlations and experimental models. *GMS Infect Dis*. 2020;8: Doc02. https://doi.org/10.3205/id000046.
46. Tchesnokova V, Larson L, Basova I, Sledneva Y, Choudhury D, Solyanik T, et al. Gut resident Escherichia coli profile predicts the eighteen-month probability and antimicrobial susceptibility of urinary tract infections. *medRxiv*. 2024; 2024.04.05.24305377. https://doi.org/10.1101/2024.04.05.24305377.
47. Worby CJ, Schreiber HL, Straub TJ, van Dijk LR, Bronson RA, Olson BS, et al. Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. *Nature Microbiology*. 2022;7(5): 630–639. https://doi.org/10.1038/s41564-022-01107-x.
48. Magruder M, Edusei E, Zhang L, Albakry S, Satlin MJ, Westblade LF, et al. Gut commensal microbiota and decreased risk for Enterobacteriaceae bacteriuria and urinary tract infection. *Gut Microbes*. 2020;12(1): 1805281. https://doi.org/10.1080/19490976.2020.1805281.
49. Urakami C, Yamanouchi S, Kimata T, Tsuji S, Akagawa S, Kino J, et al. Abnormal Development of Microbiota May Be a Risk Factor for Febrile Urinary Tract Infection in Infancy. *Microorganisms*. 2023;11(10). https://doi.org/10.3390/microorganisms11102574.
50. Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *The Lancet*. 2019;394(10196): 420–431. https://doi.org/10.1016/S0140-6736(19)31266-8.
51. Baunwall SMD, Lee MM, Eriksen MK, Mullish BH, Marchesi JR, Dahlerup JF, et al. Faecal microbiota transplantation for recurrent Clostridioides difficile infection: An updated systematic review and meta-analysis. *EClinicalMedicine*. 2020;29–30: 100642. https://doi.org/10.1016/J.ECLINM.2020.100642.
52. Ghani R, Mullish BH, Roberts LA, Davies FJ, Marchesi JR. The potential utility of fecal (or intestinal) microbiota transplantation in controlling infectious diseases. *Gut Microbes*. 2022;14(1): 2038856. https://doi.org/10.1080/19490976.2022.2038856.
53. Tariq R, Tosh PK, Pardi DS, Khanna S. Reduction in urinary tract infections in patients treated with fecal microbiota transplantation for recurrent Clostridioides difficile

For Peer Review

infection. *European Journal of Clinical Microbiology & Infectious Diseases*. 2023;42(8): 1037–1041. https://doi.org/10.1007/s10096-023-04635-4.

54. Lahtinen P, Mattila E, Anttila VJ, Tillonen J, Teittinen M, Nevalainen P, et al. Faecal microbiota transplantation in patients with Clostridium difficile and significant comorbidities as well as in patients with new indications: A case series. *World Journal of Gastroenterology*. 2017;23(39): 7174–7184. https://doi.org/10.3748/wjg.v23.i39.7174.
55. Singh R, van Nood E, Nieuwdorp M, van Dam B, ten Berge IJM, Geerlings SE, et al. Donor feces infusion for eradication of Extended Spectrum beta-Lactamase producing Escherichia coli in a patient with end stage renal disease. *Clinical Microbiology and Infection*. 2014;20(11): O977–O978. https://doi.org/10.1111/1469-0691.12683.
56. Aira A, Rubio E, Vergara Gómez A, Fehér C, Casals-Pascual C, González B, et al. rUTI Resolution After FMT for Clostridioides difficile Infection: A Case Report. *Infectious Diseases and Therapy*. 2021;10(2): 1065–1071. https://doi.org/10.1007/s40121-020-00365-8.
57. Baek OD, Hjermitslev CK, Dyreborg L, Baunwall SMD, Høyer KL, Rågård N, et al. Early Economic Assessment of Faecal Microbiota Transplantation for Patients with Urinary Tract Infections Caused by Multidrug-Resistant Organisms. *Infectious Diseases and Therapy*. 2023;12(5): 1429–1436. https://doi.org/10.1007/s40121-023-00797-y.
58. Biehl LM, Cruz Aguilar R, Farowski F, Hahn W, Nowag A, Wisplinghoff H, et al. Fecal microbiota transplantation in a kidney transplant recipient with recurrent urinary tract infection. *Infection*. 2018;46(6): 871–874. https://doi.org/10.1007/s15010-018-1190-9.
59. Bier N, Hanson B, Jiang ZD, DuPont HL, Arias CA, Miller WR. A Case of Successful Treatment of Recurrent Urinary Tract Infection by Extended-Spectrum β-Lactamase Producing Klebsiella pneumoniae Using Oral Lyophilized Fecal Microbiota Transplant. *Microbial Drug Resistance*. 2022;29(1): 34–38. https://doi.org/10.1089/mdr.2022.0031.
60. Grosen AK, Povlsen JV, Lemming LE, Jørgensen SMD, Dahlerup JF, Hvas CL. *Faecal Microbiota Transplantation Eradicated Extended-Spectrum Beta-Lactamase-Producing Klebsiella pneumoniae from a Renal Transplant Recipient with Recurrent Urinary Tract Infections*. Case Reports in Nephrology and Dialysis. 2019. p. 102–107. https://doi.org/10.1159/000502336.
61. Ghani R, Mullish BH, McDonald JAK, Ghazy A, Williams HRT, Brannigan ET, et al. Disease Prevention Not Decolonization: A Model for Fecal Microbiota Transplantation in Patients Colonized With Multidrug-resistant Organisms. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2021;72(8): 1444–1447. https://doi.org/10.1093/cid/ciaa948.
62. Hocquart M, Pham T, Kuete E, Tomei E, Lagier JC, Raoult D. Successful Fecal Microbiota Transplantation in a Patient Suffering from Irritable Bowel Syndrome and Recurrent Urinary Tract Infections. *Open Forum Infectious Diseases*. 2019;6(10). https://doi.org/10.1093/ofid/ofz398.
63. Jeney SES, Avelar-Barragan J, Whiteson K, Chang J, Dutta S, Lane F. Fecal Putative Uropathogen Abundance and Antibiotic Resistance Gene Carriage in Women With Refractory Recurrent Urinary Tract Infection Treated With Fecal Microbiota Transplantation. *Urogynecology*. 2022;28(4). https://journals.lww.com/fpmrs/fulltext/2022/04000/fecal_putative_uropathogen_abundance_and.6.aspx

For Peer Review

64. Ramos-Martínez A, Martínez-Ruiz R, Múñez-Rubio E, Valencia-Alijo A, Ferre-Aracil C, Vera-Mendoza MI. Effect of faecal microbiota transplantation on recurrent urinary tract infection in a patient with long-term suprapubic urinary catheter. *Journal of Hospital Infection*. 2020;105(2): 332–333. https://doi.org/10.1016/j.jhin.2020.01.016.
65. Stalenhoef JE, Terveer EM, Knetsch CW, van't Hof PJ, Vlasveld IN, Keller JJ, et al. Fecal microbiota transfer for multidrug-resistant gram-negatives: A clinical success combined with microbiological failure. *Open Forum Infectious Diseases*. 2017;4(2): ofx047. https://doi.org/10.1093/ofid/ofx047.
66. Steed DB, Wang T, Raheja D, Waldman AD, Babiker A, Dhere T, et al. Gram-Negative Taxa and Antimicrobial Susceptibility after Fecal Microbiota Transplantation for Recurrent Clostridioides difficile Infection. *mSphere*. 2020;5(5). https://doi.org/10.1128/mSphere.00853-20.
67. Tariq R, Tosh PK, Pardi DS, Khanna S. Reduction in urinary tract infections in patients treated with fecal microbiota transplantation for recurrent Clostridioides difficile infection. *European Journal of Clinical Microbiology & Infectious Diseases*. 2023; https://doi.org/10.1007/s10096-023-04635-4.
68. Wang T, Kraft CS, Woodworth MH, Dhere T, Eaton ME. Fecal microbiota transplant for refractory Clostridium difficile infection interrupts 25-year history of recurrent urinary tract infections. *Open Forum Infectious Diseases*. 2018;5(2). https://doi.org/10.1093/ofid/ofy016.
69. Wood N, Propst K, Yao M, Ferrando CA. Fecal Microbiota Transfer for Clostridium difficile Infection and Its Effects on Recurrent Urinary Tract Infection. *Urogynecology*. 2023;29(10). https://journals.lww.com/fpmrs/fulltext/2023/10000/fecal_microbiota_transfer_for_clostridium.5.aspx
70. Abdali ZI, Roberts TE, Barton P, Hawkey PM. Economic evaluation of Faecal microbiota transplantation compared to antibiotics for the treatment of recurrent Clostridioides difficile infection. *EClinicalMedicine*. 2020;24. https://doi.org/10.1016/j.eclinm.2020.100420.
71. Du C, Luo Y, Walsh S, Grinspan A. Oral Fecal Microbiota Transplant Capsules Are Safe and Effective for Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. 2021;55(4): 300–308. https://doi.org/10.1097/MCG.0000000000001495.
72. Ghani R, Mullish BH, Davies FJ, Marchesi JR. How to adapt an intestinal microbiota transplantation programme to reduce the risk of invasive multidrug-resistant infection. *Clinical Microbiology and Infection*. 2022;28(4): 502–512. https://doi.org/https://doi.org/10.1016/j.cmi.2021.11.006.
73. Vendrik KEW, de Meij TGJ, Bökenkamp A, Ooijevaar RE, Groenewegen B, Hendrickx APA, et al. Transmission of Antibiotic-Susceptible Escherichia coli Causing Urinary Tract Infections in a Fecal Microbiota Transplantation Recipient: Consequences for Donor Screening? *Open Forum Infectious Diseases*. 2022;9(7): ofac324. https://doi.org/10.1093/ofid/ofac324.
74. Mullish BH, Allegretti JR. The contribution of bile acid metabolism to the pathogenesis of Clostridioides difficile infection. *Therapeutic Advances in Gastroenterology*. 2021;14: 17562848211017724. https://doi.org/10.1177/17562848211017725.
75. McDonald JAK, Mullish BH, Pechlivanis A, Liu Z, Brignardello J, Kao D, et al. Inhibiting Growth of Clostridioides difficile by Restoring Valerate, Produced by the Intestinal Microbiota. *Gastroenterology*. 2018;155(5): 1495-1507.e15. https://doi.org/https://doi.org/10.1053/j.gastro.2018.07.014.

For Peer Review

76. Ubeda C, Bucci V, Caballero S, Djukovic A, Toussaint NC, Equinda M, et al. Intestinal microbiota containing Barnesiella species cures vancomycin-resistant Enterococcus faecium colonization. *Infection and Immunity*. 2013;81(3): 965–973. https://doi.org/10.1128/IAI.01197-12.
77. Pamer EG. *Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens*. Science. 2016. p. 535–538. https://doi.org/10.1126/science.aad9382.
78. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. *Trends in Immunology*. 2012;33(9): 459–466. https://doi.org/10.1016/J.IT.2012.05.003.
79. Taur Y, Pamer EG. The intestinal microbiota and susceptibility to infection in immunocompromised patients. *Current Opinion in Infectious Diseases*. 2013;26(4): 332–337. https://doi.org/10.1097/QCO.0b013e3283630dd3.
80. Keith JW, Pamer EG. Enlisting commensal microbes to resist antibiotic-resistant pathogens. *Journal of Experimental Medicine*. 2019;216(1): 10–19. https://doi.org/10.1084/jem.20180399.
81. Kim S, Covington A, Pamer EG. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens. *Immunological Reviews*. 2017;279(1): 90–105. https://doi.org/10.1111/IMR.12563.
82. Ianiro G, Murri R, Sciumè GD, Impagnatiello M, Masucci L, Ford AC, et al. Incidence of bloodstream infections, length of hospital stay, and survival in patients with recurrent clostridioides difficile infection treated with fecal microbiota transplantation or antibiotics a prospective cohort study. *Annals of Internal Medicine*. 2019;171(10): 695–702. https://doi.org/10.7326/M18-3635.
83. Ghani R, Mullish BH, McDonald JAK, Ghazy A, Williams HRT, Brannigan ET, et al. Disease Prevention Not Decolonization: A Model for Fecal Microbiota Transplantation in Patients Colonized With Multidrug-resistant Organisms. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2021;72(8): 1444–1447. https://doi.org/10.1093/cid/ciaa948.
84. Bar-Yoseph H, Carasso S, Shklar S, Korytny A, Even Dar R, Daoud H, et al. Oral Capsulized Fecal Microbiota Transplantation for Eradication of Carbapenemase-producing Enterobacteriaceae Colonization with a Metagenomic Perspective. *Clinical Infectious Diseases*. 2021;73(1): E166–E175. https://doi.org/10.1093/cid/ciaa737.
85. Abbas Y, Haggai BY, Marie MT, Sepideh P, Andrea S, J KE, et al. Fecal microbiota transplantation: current challenges and future landscapes. *Clinical Microbiology Reviews*. 2024;37(2): e00060-22. https://doi.org/10.1128/cmr.00060-22.

For Peer Review

Non antimicrobial agent	Summary of action	Advantages	Disadvantages
Methenamine Hippurate	Bacteriostatic agent through the production of formaldehyde from hexamine in the urine (23).	Tolerated orally, relatively inexpensive. Non inferior to antibiotics (24).	Systematic review: no differences between methenamine hippurate and any comparators (25).
Immunostimulants	i.e.: Uro-vaxom (Eighteen serotypes of UPEC), Uro-Vac (Six serotypes of UPEC, *Proteus mirabilis, Morganella morganii, Klebsiella pneumoniae* and *Enterococcus faecalis*) or Uromune (*Escherichia coli, K. pneumoniae, Proteus vulgaris* and *E. faecalis*). Act to prime the immune response against specific uropathogens (26).	Well, tolerated, good short term outcome data.	Systematic review: limited long-term data (27). Only act against specific bacterial strains.
Vaginal oestrogen	Maintenance of vaginal pH to prevent colonization by uropathogens (28).	Topical effects only.	Limited long term safety data, evidence primarily for post-menopausal women with limited efficacy and local side-effects (29).

For Peer Review

D-mannose	Monosaccharide isomer of glucose that may inhibit bacterial adherence to uroepithelial cells.	Well tolerated and over the counter preparation available.	No effect seen in recent RCT (30,31).
Probiotics	Restoration of the vaginal and intestinal microbiota by lactobacilli to inhibit uropathogen proliferation and infection.	Good outcomes in RCT which combined oral and vaginal probiotics (32).	No clear signal of efficacy in combined meta-analysis. Limited evidence to date (33).

Table 1: Examples of non-antimicrobial modalities utilised to prevent recurrent urinary tract infections (rUTIs).
UPEC: uropathogenic *Escherichia coli*. RCT: randomized controlled trial.

For Peer Review

Population	Number of patients	Delivery route	Outcome post FMT	Follow-up period	Year	Reference
CDI and rUTI	1	Colonoscopy	No further UTIs	12 months	2020	(56)
rCDI and recurrent UTIs	5	Colonoscopy or capsules	The median number of UTIs per patient dropped from 4 to 0.	median 126 days	2023	(57)
recurrent ESBL UTIs in transplant patient	1	Capsule	No further UTIs	36 months*	2018	(58)
Recurrent pyelonephritis	1	oral	No further MDRO UTIs	6 months	2023	(59)
recurrent ESBL UTIs in transplant patient	1	NJ-tube	One further ESBL UTI 6 days post -FMT	12 months	2019	(60)
recurrent ESBL UTIs	9	NJ tube	Statistically significant decrease in rUTIs (pre-FMT median number of UTIs = 4 ± 2 episodes, post-FMT median = 1 ± 2 episodes; P = .008; n = 9)	6 months	2021	(61)
rUTIs	1	NG tube	No further UTIs	8 months	2019	(62)
rUTIs	4	Enema	No difference in uropathogen abundance	3 months	2022	(63)

For Peer Review

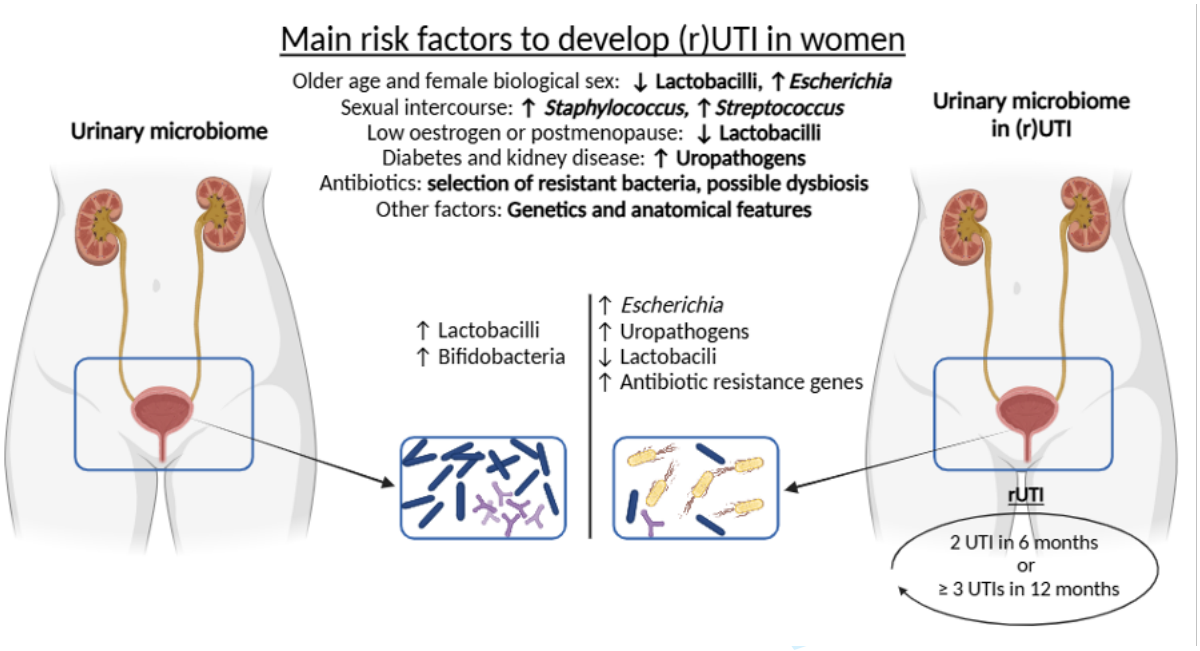
Recurrent ESBL *E. coli* pyelonephritis and rectal colonisation	1	Colonoscopy	1 episode of cystitis with fully sensitive organism. Negative faecal culture	6 weeks	2017	(54)
rCDI and rUTIs	1	Colonoscopy	No further UTIs	10 months	2020	(64)
Recurrent ESBL *E. coli* transplant pyelonephritis.	1	NJ tube	No clinical infection	3 months	2014	(55)
rUTIs in renal dialysis patient	1	NJ tube	No recurrent Pseudomonas infection One *E. coli* UTI	18 months	2017	(65)
rUTIs	6	NJ/colonoscopy.	Reduction in number of infections. Improved resistance profile of positive isolates	one year	2020	(66)
rCDI and rUTIs	8	n/a	Reduced UTI frequency No change in control group	one year	2017	(67)
rCDI and rUTIs	1	Colonoscopy	No further UTIs	25 months	2018	(68)
rCDI and rUTIs	17	Colonoscopy	A trend toward decreased frequency of UTI in the 1 year after FMT was seen in the rUTI group.	3 years	2023	(69)

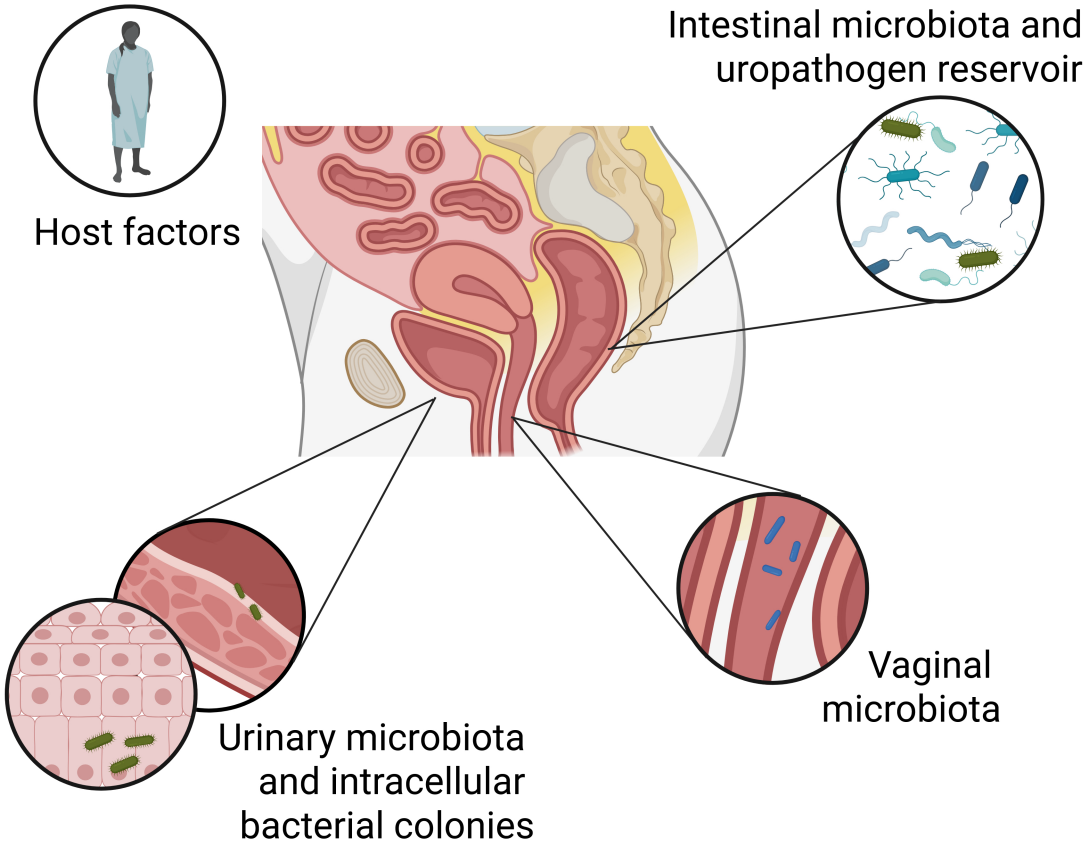
Table 2: Recent studies on the usefulness of faecal microbiota transplantation (FMT) for treating recurrent urinary tract infections (rUTIs).

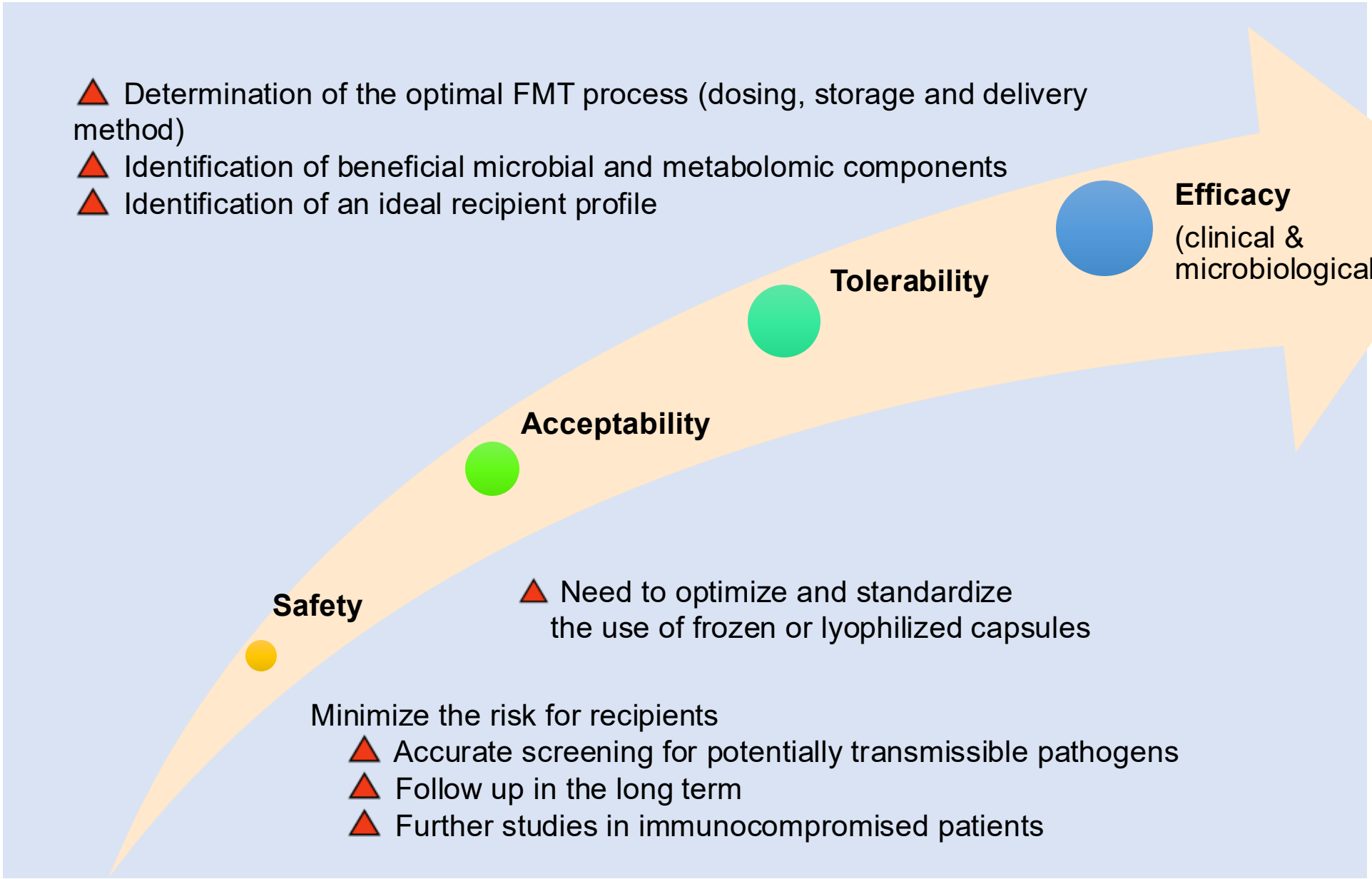
ESBL: Extended Spectrum Beta-Lactamase FMT: faecal microbiota transplantation. NG: naso-gastric, NJ: nasojejunal rCDI: recurrent *Clostridiodes difficile* infection, rUTI: recurrent urinary tract infection, UTI: urinary tract infection.

* Beyond the published follow-up, the author has followed up for 36 months and no rUTI occurred.

For Peer Review


Main risk factors to develop (r)UTI in women
Older age and female biological sex: ↓ Lactobacilli, ↑ Escherichia
Sexual intercourse: ↑ Staphylococcus, ↑ Streptococcus
Low oestrogen or postmenopause: ↓ Lactobacilli
Diabetes and kidney disease: ↑ Uropathogens
Antibiotics: selection of resistant bacteria, possible dysbiosis
Other factors: Genetics and anatomical features
Urinary microbiome
↑ Lactobacilli
↑ Bifidobacteria
↑ Escherichia
↑ Uropathogens
↓ Lactobacili
↑ Antibiotic resistance genes
Urinary microbiome in (r)UTI
rUTI
2 UTI in 6 months
or
≥ 3 UTIs in 12 months


Intestinal microbiota and uropathogen reservoir
Host factors
Vaginal microbiota
Urinary microbiota and intracellular bacterial colonies


Determination of the optimal FMT process (dosing, storage and delivery method)
Identification of beneficial microbial and metabolomic components
Identification of an ideal recipient profile
Efficacy
(clinical & microbiological)
Tolerability
Acceptability
Safety
Need to optimize and standardize the use of frozen or lyophilized capsules
Minimize the risk for recipients
Accurate screening for potentially transmissible pathogens
Follow up in the long term
Further studies in immunocompromised patients