

Original Research Article

Postbiotic Strategies and the Gut-Bladder Axis in Recurrent Urinary Tract Infection: The Butyrate-Oxygen Hypothesis, Epithelial Hypoxia and the Intestinal Uropathogen Reservoir

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Received: 11.08.2026

Accepted: 03.10.2026

Published: 14.10.2026

Journal homepage:<https://www.easpublisher.com>**Quick Response Code**

Abstract: Recurrent urinary tract infection (rUTI) affects a large proportion of women after an initial episode and consumes a substantial share of community antibiotic prescribing, yet prevention remains unsatisfactory and recurrence incompletely explained. Approximately half of recurrences are caused by the strain responsible for the index infection, implying a host reservoir that antimicrobial treatment does not eradicate. That reservoir is the intestine. This review applies to that reservoir an established mechanism that governs its size. Depletion of butyrate-producing Clostridia reduces peroxisome proliferator-activated receptor gamma signalling in colonocytes, shifts epithelial metabolism away from beta-oxidation, raises luminal oxygen and nitrate availability and permits an aerobic expansion of Enterobacteriaceae, including *Escherichia coli*. Butyrate sustains the physiological hypoxia that restrains this expansion by stabilising hypoxia-inducible factor, and the pathway is pharmacologically reversible in animal models. Women with rUTI show depletion of richness and of butyrate-producing bacteria without a corresponding difference in *E. coli* abundance, an apparent paradox that the proposed mechanism resolves, because what is lost is the epithelial capacity to restrain expansion rather than the organism itself. At population scale, butyrate-producer abundance is inversely associated with hospitalisation for infection. Antibiotics deplete these taxa profoundly and for prolonged periods, which closes a plausible self-perpetuating loop. Restoration of the intestinal community by faecal microbiota transplantation reduces recurrence. Butyrate nevertheless does not appear among interventions evaluated in current syntheses of non-antibiotic prophylaxis. We set out the evidence, state the falsifiable predictions of the model, and outline the trial required to test it. We locate butyrate-directed intervention within the wider class of postbiotic and microbial-metabolite strategies, distinguish a butyrate precursor from a postbiotic as consensus defines it, and identify sustained colonic delivery as the unresolved translational requirement.

Keywords: Butyrate - colonic microbiota - Enterobacteriaceae - epithelial hypoxia - gut-bladder axis - postbiotics - recurrent urinary tract infection - short-chain fatty acids - tributyrin.

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1. INTRODUCTION

Urinary tract infection is among the most common bacterial infections encountered in clinical practice, and its recurrent form imposes disproportionate morbidity, cost and antimicrobial exposure [1]. About a quarter of women who experience an acute episode go on to develop recurrent urinary tract infection (rUTI), and roughly half of recurrences are caused by the same strain that caused the index infection, which argues that

treatment does not clear a host-associated reservoir [2]. Prophylaxis has consequently become a major clinical preoccupation. An overview of 27 systematic reviews of randomised trials of non-antibiotic prevention in women catalogues the options that have been tested: probiotics, D-mannose, vaginal and systemic oestrogen, cranberry, methenamine hippurate, herbal preparations, increased fluid intake, acupuncture and vaccines [3]. Several are faring poorly, D-mannose among them [3].

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The clinical cost of this situation is not confined to the individual. Recurrent UTI is a major driver of community antimicrobial consumption, and repeated courses select for resistance in the organisms that cause the next episode, so that each cycle is harder to treat than the last [1,2]. Continuous low-dose prophylaxis remains effective while it is taken, but it extends rather than resolves the exposure. The field has responded by searching for non-antimicrobial alternatives, and the search has been broad rather than mechanistically directed: the interventions listed above were largely selected for plausibility and availability rather than derived from a model of why recurrence happens [3].

This review advances a mechanistic proposition that has not, to our knowledge, been applied to rUTI. The proposition is that the size and behaviour of the intestinal uropathogen reservoir are governed by colonocyte oxygen metabolism, that colonocyte oxygen metabolism is governed by microbial butyrate, and that antimicrobial therapy for rUTI degrades precisely this control system. If correct, the model reframes rUTI as a disorder in which the standard of care participates in the pathology it treats, and it identifies a class of intervention that has never been trialled for this indication.

Two clarifications frame what follows. First, the intestinal reservoir hypothesis does not displace the periurethral and vaginal route of ascent; it addresses what determines the size and composition of the population available to ascend. Second, the argument is deliberately mechanistic rather than therapeutic. No clinical trial of butyrate or of butyrate-producer restoration in rUTI exists, and none is claimed here. What is claimed is that a well-characterised control system linking microbial butyrate to intestinal *Escherichia coli* abundance has been established in other infection models, that it is reversible in those models, that its human correlates are present in rUTI, and that it has not been examined in this disease.

2. SEARCH STRATEGY

We searched an academic literature aggregator indexing PubMed, Scopus, Semantic Scholar and arXiv between 23 and 25 September 2026, using combinations of the terms *recurrent urinary tract infection*, *gut-bladder axis*, *butyrate*, *butyrate-producing bacteria*, *short-chain fatty acids*, *epithelial hypoxia*, *PPAR-gamma*, *Enterobacteriaceae expansion*, *antibiotic*, *microbiota recovery* and *non-antibiotic prophylaxis*. No language or date restriction was applied. Records were screened on title and abstract for relevance to the intestinal reservoir, to colonocyte metabolism, or to prevention of recurrence, and the reference lists of retrieved reviews were hand-searched. This is a narrative synthesis, not a systematic review, and is reported as such.

3. Relationship to companion reviews

This review is one of four by the same author group examining a single question -- whether colonic butyrate supply is a modifiable determinant of disease -- in two clinical domains where the evidence is incomplete in different ways. Because the four share a mechanistic core, the boundary between them is stated here explicitly.

Within the urinary domain, the present review sets out the forward mechanism: how depletion of butyrate-producing *Clostridia* raises epithelial oxygenation and permits the intestinal uropathogen reservoir to expand. The companion review takes the same mechanism from the opposite end and asks whether antimicrobial therapy for recurrent infection is itself the most common cause of that depletion, synthesising the human volunteer and cohort literature on microbiota recovery after antibiotic exposure and deriving a stewardship position from it [4]. The division is deliberate: this article is a mechanistic hypothesis with falsifiable predictions, that one is an assessment of iatrogenic harm with implications for prescribing. Neither depends on the other being correct, and the evidence each rest on is largely distinct.

The remaining two reviews apply the same butyrate-supply question to polyendocrine metabolic ovarian syndrome: one to the lean, insulin-resistant Indian adult phenotype [5], the other to the adolescent window in which prevention would have to occur [6]. They are cited here not for their clinical content but because all four converge on one unresolved translational problem, addressed in the translational perspective section below: no formulation of a butyrate precursor has been shown to deliver butyrate to the distal colon in humans at a concentration that the mechanism requires.

4. Recurrent urinary tract infection is a reservoir disorder

The intestine is the principal habitat of uropathogenic *Escherichia coli*, and the gut-bladder axis has become an explicit object of study [7]. In a year-long study of 15 women with and 16 women without a history of rUTI, with monthly faecal sampling and paired urine and blood, the gut microbiome of women with rUTI was significantly depleted in microbial richness and in butyrate-producing bacteria relative to controls [8]. The finding that gives the field its central difficulty appeared in the same study: *E. coli* populations in gut and bladder were comparable between cohorts in both relative abundance and phylogroup. Transcriptional profiling of peripheral blood mononuclear cells indicated differential systemic immunity, and the authors concluded that susceptibility is mediated in part through gut dysbiosis and a differential immune response to bladder colonisation rather than through a larger reservoir [7,8].

A subsequent multicentre longitudinal study of 125 patients with UTI caused by an antibiotic-resistant

organism, analysing 644 stool samples and 895 uropathogenic *E. coli* isolates, did not find a general difference between the gut microbiomes of patients with and without recurrence [9]. It did, however, report two observations of direct relevance here: the UTI gut microbiome was distinct from healthy reference microbiomes in composition and resistance-gene burden, and patients with urinary tract colonisation showed elevated gut *E. coli* abundance 7 to 14 days after antimicrobial treatment [9]. A post-antimicrobial bloom is not a baseline difference, and a model of rUTI that predicts the former without requiring the latter fits these data better than one that does not.

The reservoir framing also explains a feature of rUTI that a purely bladder-centred account does not. Recurrence clusters in time after treatment rather than being distributed at random, and the organism recovered is frequently the organism previously eradicated from the urine [2]. Either the bladder retains an intracellular population that reactivates, or the gut re-seeds the urinary tract, or both. The two are not mutually exclusive, but only the second is modifiable by anything other than a further antimicrobial, and only the second offers a mechanism through which treatment itself could raise the probability of the next episode.

5. The epithelial oxygen mechanism

Colonocytes in the healthy distal gut derive most of their energy from the beta-oxidation of microbially produced butyrate. This consumes oxygen, maintains steep epithelial hypoxia and keeps the lumen anaerobic, which in turn favours the obligate anaerobes that produce butyrate. The control point was identified directly: depletion of butyrate-producing microbes by antibiotic treatment reduced epithelial signalling through the intracellular butyrate sensor peroxisome proliferator-activated receptor gamma (PPAR-gamma), raised colonic epithelial expression of *Nos2* and luminal nitrate, and increased the bioavailability of respiratory electron acceptors to Enterobacteriaceae, permitting a dysbiotic expansion of *Escherichia* and *Salmonella* in the colonic lumen [10]. The same logic had been demonstrated in a *Salmonella* model, in which streptomycin depleted butyrate-producing Clostridia, lowered butyrate, increased epithelial oxygenation and permitted aerobic luminal expansion of the pathogen [11].

Butyrate maintains this hypoxia by more than one route. Bacteria-derived butyrate affects epithelial oxygen consumption and stabilises hypoxia-inducible factor (HIF), a transcription factor co-ordinating barrier protection; antibiotic-mediated depletion of the microbiota reduces colonic butyrate and HIF expression, and both are restored by butyrate supplementation [12]. Butyrate is additionally a direct, non-competitive inhibitor of HIF prolyl hydroxylases, with an inhibition constant of 5.3 mM, a concentration within the physiological luminal range [13]. Epithelial metabolism is therefore best understood as a switch between butyrate

beta-oxidation and anaerobic glycolysis, the latter releasing oxygen into the lumen and favouring facultative anaerobes irrespective of their pathogenic potential [14].

The identity of the electron acceptor matters for the argument. Inducible nitric oxide synthase-derived nitrate and diffusing epithelial oxygen both favour organisms capable of respiration, and Enterobacteriaceae are equipped for both¹⁰. Obligately anaerobic butyrate producers are not. A rise in epithelial oxygenation therefore does not simply permit a pathogen to grow; it reconfigures the competitive landscape in favour of the entire facultatively anaerobic fraction and against the taxa that would otherwise restore the hypoxia. This is why an expansion of Enterobacteriaceae has come to be regarded as a microbial signature of epithelial dysfunction rather than as a property of any one pathogen [14], and it is why the perturbation is self-reinforcing once established.

Why butyrate rather than short-chain fatty acids in general

Acetate, propionate and butyrate are frequently treated as a single exposure, and for this mechanism they are not interchangeable. Butyrate is the preferred oxidative substrate of the differentiated colonocyte, and it is the oxidation of butyrate specifically that consumes epithelial oxygen and generates the hypoxia that excludes facultative anaerobes [12,14]. Butyrate is also the short-chain fatty acid that acts as a direct inhibitor of HIF prolyl hydroxylase, an activity not shared equivalently by the other two [13]. A consequence for study design follows: interventions that raise total faecal short-chain fatty acids without raising butyrate delivery to the distal colon would not be expected to reproduce the effect, and trials that pool them will underestimate it.

6. The pathway is reversible

Three lines of evidence show that the mechanism is not merely descriptive. First, epithelial hypoxia and restriction of pathogen expansion were restored by tributyrin, an orally administered butyrate precursor, in the streptomycin-*Salmonella* model [11]. Second, pharmacological activation of the same receptor reproduces the effect: 5-aminosalicylic acid, a PPAR-gamma agonist, restored epithelial hypoxia and blunted dysbiotic *E. coli* expansion, and lost this capacity in animals lacking epithelial *Pparg* [15]. Third, in a fungal model the same agonist functionally replaced Clostridia in restoring epithelial hypoxia and colonisation resistance after antibiotics [16]. Protection is threshold-dependent rather than linear: in mice, restriction of Enterobacteriaceae required caecal butyrate above approximately 50 nmol/mg, and supplementation below that concentration did not protect [17]. Butyrate also acts on the epithelium independently of luminal oxygen, limiting adherent-invasive *E. coli*-evoked mitochondrial fragmentation and barrier disruption through free fatty acid receptor 3 [18].

7. From mechanism to population

If butyrate-producer abundance governs colonisation resistance, it should predict infection at scale. In two independent population-based cohorts comprising 10,699 participants, higher relative abundance of butyrate-producing bacteria was associated with a reduced risk of hospitalisation or death from infection over five to seven years of follow-up, with cause-specific hazard ratios of 0.75 (95% CI 0.60-0.94) in the derivation cohort and 0.86 (0.77-0.96) in the validation cohort per 10 per cent increase in butyrate producers [19]. These associations were unchanged after adjustment for demographics, lifestyle, comorbidity and antibiotic exposure [19]. The outcome is all-cause infectious hospitalisation rather than rUTI specifically, which is a limitation, but the direction, the magnitude and the robustness to antibiotic adjustment are consistent with the mechanism described above. Within the urinary tract, antimicrobial resistance genes are enriched in the urogenital microbiome of postmenopausal women with a history of rUTI independently of current infection status, indicating that the perturbation outlasts the episode [20].

Two features of that analysis deserve emphasis for the present argument. The association was measured against relative abundance of butyrate producers rather than against faecal butyrate concentration, which avoids the measurement problem discussed below. And the effect persisted after adjustment for antibiotic exposure, which means it is not simply a restatement of the observation that people who take more antibiotics get more infections [19].

8. Antibiotics close the loop

The taxa on which this mechanism depends are the taxa most damaged by treatment. In 12 healthy men given a four-day course of meropenem, gentamicin and vancomycin, the immediate changes included blooms of enterobacteria and other pathobionts and depletion of *Bifidobacterium* species and butyrate producers; although the community recovered to near-baseline composition within about six weeks, nine common species present in all subjects beforehand remained undetectable in most subjects at 180 days [21]. In 13 healthy men given seven days of ciprofloxacin, vancomycin and metronidazole, antibiotics significantly reduced the abundance of taxa with important metabolic functions including butyrate production, and although the microbiota returned towards baseline over 8 to 31 months, composition often remained altered [22]. The susceptibility is not uniform across agents: antibiotics directed at Gram-positive organisms are of particular concern for *Roseburia* and related butyrate producers [23].

Set beside the observation that patients colonised in the urinary tract show gut *E. coli* blooms in the one to two weeks after antimicrobial treatment [9], these data describe a loop. Antibiotic exposure depletes

butyrate producers; reduced butyrate reduces PPAR- γ and HIF signalling; the epithelium releases oxygen; Enterobacteriaceae expand; the reservoir and the probability of a further episode increase; and a further course of antibiotics follows. Each turn of the loop is individually documented. The loop as a whole has not previously been assembled.

The magnitude of the perturbation should not be understated. These were healthy young volunteers receiving short courses under controlled conditions [21,22]. Women with recurrent UTI receive repeated courses, often over years, frequently including agents active against Gram-positive anaerobes, and commonly without an intervening period long enough for the community to recover [23]. If a single four-day course leaves nine common species undetectable at six months in healthy men²¹, the cumulative effect of a decade of intermittent prophylaxis on butyrate-producing capacity is likely to be considerably greater, and has not been measured.

9. Human proof of concept and its limits

Restoring the community, rather than supplying the metabolite, has been tested. Faecal microbiota transplantation given for recurrent *Clostridioides difficile* infection was associated with a significant reduction in rUTI frequency and an improved antibiotic susceptibility profile of UTI-causing organisms [24]. More directly, a proof-of-concept study administered oral lyophilised faecal capsules to 22 postmenopausal women with rUTI after a short course of rifaximin and reported a 68.1 per cent reduction in urinary infectious episodes over six months, with eradication of faecal colonisation by multidrug-resistant uropathogens and minimal adverse effects [25]. These are uncontrolled or observational designs and cannot establish efficacy, but they demonstrate that the intestinal compartment is a modifiable determinant of urinary recurrence in humans.

10. Translational perspective: emerging postbiotic and butyrate-delivery strategies

Interest in microbiome-derived intervention has expanded beyond live probiotics to include postbiotic preparations and strategies designed to deliver microbial metabolites, or their precursors, to defined intestinal sites. Precision about the category is necessary before proceeding. A postbiotic was defined by international consensus as a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host [26], and isolated or purified metabolites fall outside that definition [27]. Glycerol tributyrate (tributylin), a triglyceride ester of butyric acid, is therefore not a postbiotic in the consensus sense: it contains no microbial cells or cell components. It is a butyrate precursor, and it is discussed alongside postbiotic approaches here because the two act on the same host pathway and are being developed for the same clinical purpose, not because they belong to the same regulatory or definitional category.

Tributylin has already served as the proof-of-mechanism butyrate precursor for the pathway described in this review. In the streptomycin-*Salmonella* model, orally administered tributyrin restored epithelial hypoxia and restricted the aerobic luminal expansion of the pathogen [11], and the reversibility of the pathway in that experiment is the single strongest argument that the mechanism is causal rather than correlative. Whether a clinically practical formulation of glycerol tributyrate can reproduce a relevant intestinal exposure in humans with recurrent urinary tract infection is a separate question, and it is unanswered. The only published human study of a tributyrin complex enrolled 29 healthy adults rather than patients; the preparation was well tolerated, but faecal acetate and propionate decreased rather than increased, triglycerides rose at the higher dose, and the authors interpreted the pattern as butyrate generation and absorption in the small intestine [28]. For a mechanism that requires butyrate at the distal colonic epithelium, proximal release is not a partial success but a miss, which makes formulation the rate-limiting translational variable rather than an implementation detail.

Aeon Formulations Pvt Ltd has developed a patented technology, designated GTB, comprising a microencapsulated powder form of glycerol tributyrate, and this technology is used in the development of the ThirdBiome platform. Microencapsulation is intended to alter where in the gastrointestinal tract the ester is hydrolysed, and therefore how much butyrate reaches the distal intestine; whether it does so in humans is an empirical question that has not been answered for this or, with the single exception noted above, for any comparable preparation. Microencapsulated glycerol tributyrate technologies, including the patented GTB technology developed by Aeon Formulations Pvt Ltd and used in the development of the ThirdBiome platform, represent one formulation approach that could be evaluated against the mechanistic hypothesis advanced here. The relevance of any such delivery system to this mechanism is hypothesis-generating and not established: improved intestinal delivery of a butyrate precursor could in principle influence colonocyte oxidative metabolism, peroxisome proliferator-activated receptor gamma and hypoxia-inducible factor signalling, and the luminal availability of respiratory electron acceptors to Enterobacteriaceae, but each of those steps would have to be demonstrated. The specific efficacy of that or any other preparation in recurrent urinary tract infection requires direct clinical evaluation and cannot be inferred from the mechanistic or preclinical evidence assembled in this review. The authors' commercial interest in this technology is declared in the competing interests statement.

11. Evidence against the model

Three findings constrain it and should be stated plainly. First, the multicentre cohort described above did not reproduce a general rUTI-associated microbiome

difference [9]; the model survives only because it predicts a post-treatment expansion rather than a constitutive one, and that is a prediction requiring prospective test rather than a defence. Second, the metabolite may not be the mediator. In antibiotic-treated mice, faecal transplantation protected against *E. coli* cystitis through the tryptophan derivative indole-3-propionic acid acting on the aryl hydrocarbon receptor and inducing urothelial *Prg4*, with no butyrate-dependent step identified [29]. Butyrate producers may therefore be a marker of an intact anaerobic community whose protective output is broader than butyrate alone. Third, the measurement on which much of the observational literature rests is unreliable: luminal and faecal short-chain fatty acid concentrations do not reflect production rates and should not be used as a proxy for them [30]. Studies reporting unchanged faecal butyrate in rUTI therefore cannot exclude reduced production.

A fourth constraint is the species gap. Every step of the mechanistic chain has been demonstrated in mice, and in models of enteric rather than urinary infection: *Salmonella*, *Candida* and colitis-associated *E. coli* [10,11,15,16]. The human evidence is observational and concerns association rather than causation [8,19]. This review is therefore a hypothesis assembled from established components, not a synthesis of direct evidence, and should be read as such. Its value lies in identifying an untested and biologically plausible intervention class, and in specifying how it could be refuted.

12. Falsifiable predictions and the trial that follows

A hypothesis earns its place by being refutable. The model predicts, first, that women with rUTI will show reduced faecal butyrate-producer gene abundance and reduced epithelial hypoxia markers rather than increased steady-state *E. coli*; second, that intestinal *E. coli* expansion after an antibiotic course will be greatest in those with the lowest pre-treatment butyrate-producing capacity; third, that restoring butyrate delivery to the distal colon will blunt that expansion; and fourth, that any protective effect will be threshold-dependent rather than dose-linear [17].

The trial these predictions imply is a randomised, placebo-controlled study in women with recurrent UTI, in which a colonic-release butyrate donor or a butyrogenic fibre is given during and after an index antibiotic course. The primary endpoint should be time to next microbiologically confirmed episode. Mechanistic endpoints should include metagenomic butyryl-CoA transferase gene abundance and quantified intestinal Enterobacteriaceae, with plasma rather than faecal short-chain fatty acids as the mediator measure, since faecal concentration is not a measure of production [30]. Stratification by recent antibiotic exposure is essential, because the model predicts the largest effect in the most recently treated.

13. Implications for current practice

Nothing in this review supports prescribing butyrate, a butyrate prodrug or any specific preparation for the prevention of recurrent UTI. The evidence does not exist, and the appropriate conclusion from an untested hypothesis is a trial, not a prescription. Two implications are nevertheless defensible now. The first concerns antimicrobial choice: where agents of comparable efficacy are available, the differential impact on obligate anaerobes is a legitimate consideration, and is rarely one that enters the decision²³. The second concerns measurement. Faecal short-chain fatty acid panels are increasingly available to clinicians and are being used to infer colonic fermentation. Because faecal concentration reflects the balance of production, absorption and transit rather than production itself, a normal faecal butyrate result does not exclude impaired butyrate production, and should not be reported or interpreted as though it does [30].

14. CONCLUSIONS

Recurrent urinary tract infection is treated as a bladder disorder and managed with agents that degrade the intestinal community governing the reservoir from which it is repopulated. The mechanistic chain connecting butyrate-producer depletion to Enterobacteriaceae expansion is established in enteric infection models and is reversible in those models, and butyrate-producer abundance predicts infectious hospitalisation at population scale. The chain has not been tested in the urinary tract, and butyrate does not appear among the interventions evaluated in current syntheses of non-antibiotic prophylaxis [3]. A 2025 review of recurrent infection has separately observed that affected women tend to carry the lowest abundance of butyrate-producing gut bacteria and that antibiotic exposure favours uropathogen outgrowth [31]. What that literature stops short of doing is naming the epithelial mechanism that would connect the two observations, specifying the order in which its steps must occur, and stating what observation would refute it. That is the work this article attempts. That absence, rather than any claim of proven efficacy, is this review's argument: the mechanism with the most direct preclinical link to intestinal *Escherichia* expansion is the one mechanism that has not been given a trial.

15. Acknowledgements

The authors thank colleagues at ThirdBiome and at Aeon Formulations Pvt Ltd, whose work on the

microencapsulation of glycerol tributyrates informed the discussion of delivery form in the translational perspective section. Neither organisation had any role in the literature search, in the selection or appraisal of evidence, or in the decision to submit this manuscript.

16. DECLARATIONS

Competing Interests

The authors are founding members of ThirdBiome and are associated with Aeon Formulations Pvt Ltd, which has developed a patented microencapsulated glycerol tributyrates (GTB) technology used in the development of the ThirdBiome platform. These relationships constitute a financial interest in the subject matter of this review and are the reason for the disclosure that follows. The GTB technology and the ThirdBiome platform are named once, in the translational perspective section, as one example of a butyrate-delivery formulation approach. No efficacy claim is made for either, no unpublished or proprietary data from either organisation are reported, and no recommendation for clinical use is given anywhere in this article. Neither organisation funded this review, had any role in its design, conduct, literature identification, evidence appraisal or reporting, or reviewed the manuscript before submission. The authors confirm that every evidence assessment in this review reflects the published literature independently of these commercial interests.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author Contributions: V.A.: conceptualisation, methodology, investigation, writing - original draft, writing - review and editing, supervision. J.S.: investigation, formal analysis, writing - review and editing. Both authors approved the final manuscript.

Ethical Clearance: Not applicable. This is a narrative review of published literature. No human participants, human material or human data were involved, and no institutional ethics committee approval was required.

Data Availability: No new data were generated. The search strategy is described in the manuscript; the full list of retrieved records is available from the corresponding author on reasonable request.

Table I: The proposed causal chain in recurrent urinary tract infection and the strength of evidence for each step

Step in the chain	Principal evidence	Evidence level
Antibiotic exposure depletes butyrate-producing taxa	Human volunteer studies; some species undetectable at 180 days [21, 22]	Human, experimental
Depleted butyrate reduces colonocyte PPAR-gamma and HIF signalling	Murine and cell-based studies [10, 12, 13]	Animal, mechanistic
Loss of epithelial hypoxia raises luminal oxygen and nitrate	Murine colonisation models [10, 11, 14]	Animal, mechanistic

Step in the chain	Principal evidence	Evidence level
Enterobacteriaceae including <i>Escherichia</i> expand aerobically	Murine Salmonella and <i>E. coli</i> models [10, 11, 15]	Animal, mechanistic
Expansion is reversible with tributyrin or PPAR-gamma agonism	Murine rescue experiments [11, 15, 16]	Animal, interventional
Protection is threshold-dependent	Caecal butyrate above ~50 nmol/mg required [17]	Animal, dose-response
Butyrate producers are depleted in women with rUTI	Year-long longitudinal cohort [8]	Human, observational
Gut <i>E. coli</i> blooms after antimicrobial treatment in colonised patients	Multicentre longitudinal cohort [9]	Human, observational
Butyrate-producer abundance predicts infectious hospitalisation	Two population cohorts, n=10,699 [19]	Human, prospective
Restoring the community reduces recurrence	FMT cohort and proof-of-concept study [24, 25]	Human, uncontrolled

Table II: Predictions of the model, and the observations that would refute it

Prediction	Design able to test it	Refuting observation
Butyrate-producing gene abundance is reduced in rUTI independently of <i>E. coli</i> abundance	Case-control metagenomics with matched antibiotic and dietary history	No difference in butyryl-CoA transferase gene abundance between cases and matched controls
Post-antibiotic intestinal <i>E. coli</i> expansion is greatest where butyrate-producing capacity is lowest	Prospective cohort sampled before and serially after a treated episode	Expansion unrelated to baseline butyrate-producing capacity
Colonic butyrate restoration blunts post-antibiotic Enterobacteriaceae expansion	Randomised, placebo-controlled challenge with a colonic butyrate donor	No difference in expansion between butyrate donor and placebo
The effect is threshold-dependent	Dose-ranging arm nested within the same trial	A linear dose-response, or benefit at concentrations well below the animal threshold
Plasma rather than faecal butyrate tracks the effect	Paired plasma and faecal measurement within any of the above	Faecal butyrate tracks clinical outcome while plasma butyrate does not

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Cite This Article: Ariarasudhan, V., & Jayavardhini, S. (2026). Postbiotic Strategies and the Gut-Bladder Axis in Recurrent Urinary Tract Infection: The Butyrate-Oxygen Hypothesis, Epithelial Hypoxia and the Intestinal Uropathogen Reservoir. *East African Scholars J Med Surg*, 8(9), 362-369. <https://doi.org/10.36349/easjms.2026.v08i09.001>