

Postbiotic Strategies after Antibiotic Exposure in Recurrent Urinary Tract Infection: The Antibiotic Paradox, Butyrate-Producing Bacteria and Microbiome Recovery

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Abstract

Review Article

Recurrent urinary tract infection (rUTI) is managed with repeated, and often continuous, antimicrobial therapy. This review examines whether that strategy contributes to the condition it treats. We synthesise human volunteer and cohort studies of gut microbiota recovery after antibiotic exposure with the emerging evidence that butyrate-producing intestinal bacteria govern colonisation resistance against Enterobacteriaceae. Across controlled human studies, obligately anaerobic butyrate producers are among the taxa most consistently depleted and slowest to recover: community composition returns towards baseline within weeks to a few months, but individual species present in every participant before exposure can remain undetectable at 180 days, and compositional change has been documented between eight and 31 months after a single course. Recovery is not uniform across agents, and is modified by host diet and by repeat exposure. The functional consequence is relevant to urinary infection specifically, because depletion of these taxa reduces colonocyte oxidative metabolism and permits aerobic expansion of intestinal *Escherichia coli*, the reservoir from which most recurrences arise. Women with rUTI show depletion of butyrate producers, and intestinal *E. coli* blooms have been documented in the one to two weeks after antimicrobial treatment in patients colonised in the urinary tract. Together these observations describe a plausible iatrogenic loop. We assess what can and cannot be concluded, identify the agents least damaging to anaerobes, evaluate whether recovery can be accelerated, and propose a stewardship position for recurrent UTI that treats the intestinal anaerobic community as a tissue worth protecting. We place postbiotic and butyrate-precursor approaches within the set of candidate restoration strategies, and state what each would have to demonstrate before it could be offered to this population.

Keywords Antimicrobial stewardship - butyrate-producing bacteria - colonisation resistance - gut microbiota - microbiome recovery - postbiotics - recurrent urinary tract infection - tributyrin.

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1. INTRODUCTION

Antimicrobial therapy for urinary tract infection is effective, evidence-based and, for the acute episode, not seriously disputed. The difficulty arises in the recurrent form. Roughly a quarter of women with an acute episode develop recurrent urinary tract infection (rUTI), and management then shifts from treating episodes to preventing them, commonly with repeated short courses or with continuous low-dose prophylaxis [1,2]. Continuous prophylaxis is effective while it is taken and its benefit does not reliably persist after it stops [3]. The clinical logic is therefore circular in a way that is rarely made explicit: the intervention suppresses

recurrence without addressing the state that produces it, and is continued for that reason.

A stronger version of the concern has begun to appear in the urological literature, which now describes women with rUTI as caught in a cycle in which antibiotics given to eradicate one infection predispose them to the next, mediated by disturbance of the gut microbiome [4]. The search for alternatives has been correspondingly broad: an overview of 27 systematic reviews of randomised trials catalogues ten distinct non-antibiotic strategies tested in women with recurrent infection [5]. This review tests that proposition against the human evidence on antibiotic-induced microbiota

perturbation, with a specific focus on the obligately anaerobic butyrate-producing taxa that have emerged as the functional link between the intestinal community and resistance to Enterobacteriaceae. Our purpose is not to argue against treating urinary infection. It is to ask whether the collateral cost of treatment is being counted, and whether it can be reduced.

The question has become more pressing for two reasons. Antimicrobial resistance among uropathogens has risen to the point where the agents available for an uncomplicated episode are fewer than a decade ago, and each course of prophylaxis contributes to that trajectory [1]. Separately, the gut has been established as the reservoir from which most recurrences arise, which means that the collateral effect of treatment falls on the very compartment that determines susceptibility [2,4]. A collateral effect on a bystander organ is a tolerable cost; a collateral effect on the organ that governs recurrence is a different proposition and deserves separate examination.

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 *antibiotic*, *gut microbiota recovery*, *resilience*, *butyrate-producing bacteria*, *674 rioritized* *674 resistance*, *recurrent urinary tract infection*, *antimicrobial stewardship* and *674 rioritiz*. Human studies reporting longitudinal sampling before and after a defined antibiotic exposure were 674rioritized for the recovery synthesis; animal and mechanistic studies were retained only where they explain a human observation. Reference lists of retrieved reviews were hand-searched. This is a narrative synthesis; the recovery data in Table I are tabulated but not pooled, because heterogeneity of agent, dose, duration, sampling interval and sequencing method precludes meta-analysis.

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.

The companion review in the urinary domain establishes the forward mechanism this article assumes: that depletion of butyrate-producing Clostridia reduces colonocyte peroxisome proliferator-activated receptor gamma signalling, raises epithelial oxygenation and permits aerobic expansion of intestinal *Escherichia coli*, and that the pathway is reversible in animal models [6]. The present article takes that mechanism as given and asks a different and more immediately actionable question: what antimicrobial therapy does to those taxa, how long the damage lasts, which agents cause least of it, and what should therefore change in prescribing. The

evidence base is correspondingly different -- controlled human volunteer studies of microbiota recovery rather than murine infection models -- and the two reviews can be read independently.

The other two reviews in the series apply the same butyrate-supply question outside infection, to the Indian adult polyendocrine metabolic ovarian syndrome phenotype [7] and to prevention in adolescence [8]. All four arrive at the same translational bottleneck, considered below: substrate supply and metabolite delivery are different interventions, and the formulation that determines which one is actually being given has not been characterised in humans.

4. What antibiotics do to butyrate-producing bacteria

The controlled human evidence is small in participant numbers but unusually consistent. In 12 healthy men given four days of meropenem, gentamicin and vancomycin, the immediate response included blooms of enterobacteria and other pathobionts with depletion of *Bifidobacterium* species and butyrate producers; the community recovered to near-baseline composition within about six weeks, yet nine common species present in all participants beforehand remained undetectable in most of them at 180 days [9]. In 13 healthy men given seven days of ciprofloxacin, vancomycin and metronidazole, the short-term impact was profound, with loss of diversity and a significant reduction in taxa with important metabolic functions including butyrate production; the microbiota showed a remarkable return towards baseline at eight to 31 months, but composition often remained altered from its initial state [10].

Single-agent studies show the same pattern with different kinetics. Oral vancomycin depleted most genera including all baseline operational taxonomic units of the phylum Bacteroidetes, with expansion of *Klebsiella* and *Escherichia/Shigella*; resilience varied markedly between individuals, and in some, up to 89 per cent of abundant taxa could no longer be detected 22 weeks after cessation [11]. Ten days of ciprofloxacin or clindamycin required between one and 12 months for normalisation depending on the taxon, with clindamycin the more disruptive [12]. Repeated exposure compounds the effect: two courses of ciprofloxacin in the same individuals produced loss of diversity within three to four days, incomplete return after each course, and a final community stabilised in an altered state [13]. Across four commonly used regimens followed for six months, most participants regained species richness by two months but with altered taxonomy, resistome and metabolic output, and a subset sustained a persistent reduction in diversity [14].

Two syntheses place these findings in context. A systematic review of antibiotic effects across body sites found consistent changes with quinolones and metronidazole and concluded that combination treatment

may produce longer-term dysbiosis [15], and a broader review of perturbation biology sets out why recovery depends on the nature, timing, duration and spectrum of the course as well as on host factors [16,17].

Three features of this literature should temper confidence. Sample sizes are small, typically between three and 25 participants, because the studies are intensive longitudinal designs rather than epidemiological ones. Participants are predominantly healthy young men, which is close to the opposite of the rUTI population. And sequencing methods, sampling intervals and definitions of recovery differ so widely that quantitative pooling is not defensible; Table I therefore tabulates rather than pools [15,16]. What the studies share, despite these differences, is the direction and the ordering of the effect: butyrate-producing anaerobes fall early, fall far, and return late.

5. Why these taxa in particular

Two properties make butyrate producers unusually vulnerable. They are obligate anaerobes, so they cannot exploit the oxygenated luminal environment that follows epithelial disruption, whereas facultatively anaerobic Enterobacteriaceae can [18,19]. And many belong to Gram-positive clostridial clusters, so they fall within the spectrum of agents chosen for Gram-positive cover; *Roseburia* and related genera are specifically noted as at risk from Gram-positive-directed prescribing [20]. The result is a selective loss rather than a proportionate one: the community may regain richness while remaining functionally impoverished in precisely the metabolic capacity that restrains the organisms responsible for urinary infection.

This matters because the loss is self-perpetuating. Depletion of butyrate-producing Clostridia reduces colonocyte signalling through peroxisome proliferator-activated receptor gamma, shifts epithelial metabolism away from oxygen-consuming beta-oxidation, raises luminal oxygen and nitrate, and permits aerobic expansion of *Escherichia* [18,19]. The expanded facultative anaerobes then sustain the oxygenated state that suppresses the return of the obligate anaerobes. Recovery is therefore not simply a matter of waiting.

6. Does the loop operate in recurrent urinary tract infection?

Three human observations are consistent with it. Women with a history of rUTI show gut microbiomes significantly depleted in richness and in butyrate-producing bacteria compared with controls [21]. In a multicentre longitudinal cohort of patients with antibiotic-resistant urinary infection, those colonised in the urinary tract showed elevated gut *Escherichia coli* abundance seven to 14 days after antimicrobial treatment, and the authors concluded that cross-habitat migration of uropathogenic *E. coli* is an important mechanism of recurrence [22]. And at population scale, higher relative abundance of butyrate producers is

associated with a lower risk of hospitalisation for infection across two cohorts totalling 10,699 participants, with the association robust to adjustment for antibiotic exposure [23].

None of this establishes causation, and the same multicentre cohort found no general difference between the gut microbiomes of patients with and without recurrence [22]. What the evidence supports is narrower and still clinically consequential: that antimicrobial treatment of urinary infection reliably damages a community whose depletion is associated with urinary infection, and that the damage outlasts the therapeutic benefit by months.

A distinction between compositional and functional recovery is therefore essential, and much of the reassurance in this literature rests on conflating them. Reports that the microbiota 'recovers within weeks' generally refer to alpha diversity or overall community structure. Studies that looked specifically found altered taxonomy, resistome and metabolic output persisting well beyond the point at which richness had normalized [14], and species-level absences at six months in participants whose community-level indices had returned to baseline [9]. For a mechanism that depends on the metabolic output of a particular functional guild rather than on diversity as such, community-level recovery is the wrong endpoint.

7. What modifies recovery

Recovery is not fixed. In a controlled comparison isolating diet, treatment history and housing, a fibre-deficient diet exacerbated microbiota collapse and delayed recovery, while prior species replacement conferred resilience to a second course [24]. This is directly relevant to rUTI populations, in whom dietary fibre intake is rarely assessed and frequently low, and it suggests that the same antibiotic course may carry materially different collateral cost in different patients. Choice of agent also matters. A systematic review of the antibiotics most commonly prescribed in UK primary care found that doxycycline and clarithromycin produced marked and prolonged changes, whereas phenoxymethylpenicillin, amoxicillin and, notably for this indication, nitrofurantoin had very little effect on the gut microbiome [25].

8. Can recovery be accelerated?

Two approaches have human data. In a randomised placebo-controlled trial in healthy adults receiving seven days of ciprofloxacin and metronidazole, a multi-species synbiotic given for 91 days enhanced recovery of native butyrate-producing species and raised faecal butyrate by 119 per cent and faecal acetate by 62 per cent relative to placebo, with improved gut barrier integrity at both day 7 and day 91 [26]. This is a proof-of-mechanism study in healthy volunteers with no clinical infection endpoint, and should not be read as evidence of clinical benefit. Second, whole-community

restoration has been associated with reduced urinary recurrence: faecal microbiota transplantation given for recurrent *Clostridioides difficile* infection reduced rUTI frequency and improved antibiotic susceptibility profiles [27], and an uncontrolled proof-of-concept study in 22 postmenopausal women with rUTI reported a 68.1 per cent reduction in urinary infectious episodes over six months [28]. Neither design can establish efficacy, and faecal transplantation is not a realistic population-level intervention for this indication.

The nitrofurantoin observation deserves particular attention in this population, because nitrofurantoin is already widely used for uncomplicated urinary infection and for prophylaxis, is concentrated in urine with limited systemic exposure, and on the available evidence appears to spare the colonic community to a degree that fluoroquinolones and broad-spectrum agents do not [25]. If the loop described in this review is real, the agent already preferred on resistance grounds may also be the agent that least perpetuates the underlying susceptibility. That is a testable proposition and, unusually for this field, one that requires no new drug.

9. 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 [29], and isolated or purified metabolites fall outside that definition [30]. Glycerol tributyrinate (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.

Candidate restoration strategies fall into five groups: dietary substrate provision, prebiotic supplementation, synbiotic intervention, whole-community restoration, and direct delivery of butyrate or a butyrate precursor. Only the third and fourth have human data in or adjacent to this context, and both are preliminary [26-28]. Direct precursor delivery is the least evidenced of the five in humans and the best evidenced in animals. In antibiotic-treated mice, tributyrin increased alpha diversity, raised short-chain fatty acid concentrations, expanded short-chain fatty acid-producing taxa including *Bifidobacterium*, suppressed potentially pathogenic taxa including *Enterococcus*, lowered serum lipopolysaccharide and zonulin, and

upregulated tight-junction proteins and MUC2 [31]. That is close to the profile a restoration agent for this indication would need. The human counterpart is weaker: the only published pilot study of a tributyrin complex was conducted in healthy adults with no antibiotic exposure and no clinical endpoint, and it reported decreased faecal acetate and propionate with a pattern suggesting small-intestinal release [32]. The animal result establishes that the strategy can work; the human result establishes that a given formulation may not.

Aeon Formulations Pvt Ltd has developed a patented technology, designated GTB, comprising a microencapsulated powder form of glycerol tributyrinate, 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. The GTB technology developed by Aeon Formulations Pvt Ltd and incorporated into the ThirdBiome platform is one example of such a delivery strategy. Its ability to accelerate functional microbiome recovery after antimicrobial exposure has not been established clinically and is not claimed here. Establishing it would require a randomised placebo-controlled trial in the population defined in the research agenda below, with metagenomic butyryl-CoA transferase gene abundance rather than faecal short-chain fatty acid concentration as the mediator endpoint, and with recurrence as the clinical one. Until such a trial exists, the defensible position for this review is that direct precursor delivery is a testable hypothesis within an under-tested category, and that the stewardship measures set out next, which require no new product, are what the present evidence supports. The authors' commercial interest in this technology is declared in the competing interest's statement.

10. A stewardship position for recurrent urinary tract infection

Antimicrobial stewardship has historically been framed around resistance. The evidence reviewed here suggests a second and complementary rationale in this population: preservation of the anaerobic community that contributes to colonisation resistance. Four positions follow, and we grade them honestly in Table II. Where agents of comparable clinical efficacy are available, those with the least anaerobic impact should be preferred, and nitrofurantoin compares favourably on the available microbiome data [25]. Duration should be minimised rather than extended by default, since depth of perturbation tracks duration and spectrum [15,17]. Continuous prophylaxis should be time-limited and reviewed, with the collateral cost stated to the patient as part of consent [3,4]. And dietary fibre intake, which modifies recovery in controlled conditions [24], is a low-

risk adjunct that is currently not part of routine advice for this group.

We emphasise what does not follow. Nothing here justifies withholding antimicrobial treatment from a symptomatic urinary infection, delaying treatment of

pyelonephritis, or substituting an unproven microbiome-directed intervention for effective therapy. The argument is about the choice between broadly equivalent antimicrobials, the duration of exposure, and what is measured and discussed alongside it.

Table I: Human studies of gut microbiota recovery after antibiotic exposure, with findings relevant to butyrate-producing taxa

Study	Exposure	n; follow-up	Findings relevant to butyrate producers
Dethlefsen & Relman ¹³	Ciprofloxacin, two courses	3; 10 months	Diversity lost within 3-4 days; return began within a week of each course but was incomplete; final community altered
Rashid <i>et al</i> ¹²	Ciprofloxacin or clindamycin, 10 days	n=25; 12 months	Normalisation required 1-12 months depending on taxon; clindamycin more disruptive than ciprofloxacin
Isaac <i>et al</i> ¹¹	Oral vancomycin	n=6; 22 weeks	Depletion of most genera with expansion of <i>Klebsiella</i> and <i>Escherichia/Shigella</i> ; up to 89% of abundant taxa undetectable in some individuals
Palleja <i>et al</i> ⁹	Meropenem, gentamicin, vancomycin, 4 days	12; 180 days	Depletion of butyrate producers and <i>Bifidobacterium</i> ; near-baseline recovery by ~6 weeks but 9 common species undetectable in most at 180 days
Haak <i>et al</i> ¹⁰	Ciprofloxacin, vancomycin, metronidazole, 7 days	13; 8-31 months	Significant reduction in taxa with butyrate-producing function; return towards but not to baseline
Anthony <i>et al</i> ¹⁴	Four common regimens	n=20; 6 months	Richness recovered by ~2 months in most, with altered taxonomy, resistome and metabolic output; azithromycin delayed recovery; persistent reduction in a subset
Elvers <i>et al</i> ²⁵	Primary-care agents (systematic review)	31 studies	Doxycycline and clarithromycin produced marked, prolonged change; nitrofurantoin, amoxicillin and phenoxymethylpenicillin had very little effect
Napier <i>et al</i> ²⁶	Ciprofloxacin + metronidazole 7 days, with synbiotic or placebo	RCT; 91 days	Synbiotic enhanced recovery of native butyrate producers; faecal butyrate +119% and acetate +62% versus placebo

Table II: Stewardship positions for recurrent urinary tract infection, graded by the strength of the evidence supporting them

Position	Basis	Strength
Prefer agents with least anaerobic impact where clinical efficacy is comparable	Systematic review of primary-care agents ²⁵	Moderate; indirect for rUTI outcomes
Minimise duration and spectrum rather than extending by default	Depth of perturbation tracks duration and spectrum ^{15,17}	Moderate
Time-limit and review continuous prophylaxis; state the collateral cost in consent	Prophylaxis benefit does not persist after cessation ^{3,4}	Consensus, not trial-based
Assess and support dietary fibre intake during and after courses	Fibre-deficient diet delayed recovery under controlled conditions ²⁴	Weak in humans; low risk
Do not substitute microbiome-directed intervention for indicated antimicrobial therapy	No clinical efficacy data in rUTI	Strong

11. Limitations

This review has three principal limitations. It is narrative rather than systematic, and the recovery studies summarised in Table I were identified through a targeted rather than an exhaustive search; a registered systematic review with quantitative synthesis would be the appropriate next step and is not attempted here. The human recovery data derive almost entirely from healthy

volunteers receiving single defined courses, whereas the population of concern receives repeated courses over years, so the cumulative effect is inferred rather than observed. And the link between butyrate-producer depletion and urinary recurrence remains associative: no study has demonstrated that restoring these taxa reduces recurrence, and the one mechanistic animal study to examine faecal transplantation in cystitis identified a

tryptophan derivative rather than butyrate as the protective mediator.

12. Research agenda

The most useful next study is not a trial but a measurement. No study has quantified butyrate-producing capacity longitudinally in women receiving repeated or continuous antimicrobial prophylaxis for rUTI, which is the population in whom the hypothesised cumulative effect should be largest and in whom it has never been looked for. Such a cohort, using metagenomic butyryl-CoA transferase gene abundance rather than faecal short-chain fatty acid concentration, would establish whether the loop described here operates at clinically relevant magnitude. A randomised comparison of nitrofurantoin against a more anaerobe-active comparator, with microbiome endpoints alongside clinical ones, would test the stewardship proposition directly and could be nested within existing prophylaxis practice.

13. CONCLUSIONS

Antimicrobial therapy for recurrent urinary tract infection depletes obligately anaerobic butyrate-producing bacteria substantially, selectively and for longer than the treatment itself, and these are the taxa whose depletion is associated with recurrent urinary infection and with infectious hospitalisation at population scale. Whether this constitutes a causal iatrogenic loop remains unproven and is testable. In the interim, the collateral cost of antimicrobial exposure in this population is measurable, differs between agents, is modifiable by diet, and is not currently counted in the decision. Counting it would be a reasonable first step.

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15. 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.

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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.

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