Gut microbiota and oxalate homeostasis

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Abstract: This perspective focuses on how the gut microbiota can impact urinary oxalate excretion in the context of hyperoxaluria, a major risk factor in kidney stone disease. In the genetic disease of Primary Hyperoxaluria Type 1 (PH1), an increased endogenous production of oxalate, due to a deficiency of the liver enzyme alanine-glyoxylate aminotransferase (AGT), results in hyperoxaluria and oxalate kidney stones. The constant elevation in urinary oxalate in PH1 patients ultimately leads to tissue deposition of oxalate, renal failure and death and the only known cure for PH1 is a liver or liver-kidney transplant. The potential impact of a probiotic/therapeutic approach may be clinically significant in PH1 and could also extend to a much larger population of idiopathic oxalate stone formers who comprise ~12% of Americans, individuals with enteric hyperoxaluria, and an emerging population of hyperoxaluric patients who have undergone bariatric surgery and develop kidney stone disease as a consequence.

Keywords: *Bifidobacterium sp*.; intestinal oxalate transport; *lactobacillus sp*.; *Oxalobacter sp*.; urinary oxalate excretion; small intestine; caecum; distal colon; hyperoxaluria; hyperoxalemia; urolithiasis

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Introduction

Approximately 80% of stone forming individuals form calcium oxalate stones and hyperoxaluria is a major risk factor in this kidney disease (1,2). Oxalate is considered a useless end-product of mammalian metabolism and urinary oxalate is derived from endogenous metabolic sources, mainly produced by the liver (3), but also by dietary absorption of oxalate that can contribute as much as 50% of what is in urine (4). While urinary oxalate concentrations are in the millimolar range with an average of 0.25 mmoles/24 h in healthy controls, hyperoxaluria is defined by a urinary excretion greater than 0.45 mmoles/24 h (1,2,5). Blood levels of oxalate are several orders of magnitude lower and typically reported to be regulated at much less than 5 µM in normal healthy individuals (2,6-12). Thus, the epithelial barriers of the intestine and nephron mediate oxalate balance. In recent years, it has also been acknowledged that gut commensal bacteria with oxalate-degrading activity have the potential to contribute to oxalate homeostasis and this aspect is the focus of the current perspective. A number of published reviews with sub-sections on the role of oxalate-degrading bacteria are recommended reading, as background information, for the current perspective (13-18) which includes new and unpublished information from the author's laboratory. This is not intended to be a review of the literature.

Physiological relevance of the oxalate-degrading commensal bacteria in rodents

Oxalobacter sp.

The most commonly described intestinal bacteria known to degrade oxalate are categorized into two groups: (I) the "generalist oxalotrophs", including some strains of *Bifidobacterium* and *Lactobacillus*, that degrade alternative carbon sources in addition to oxalate; and (II) the "specialist oxalotrophs", such as *Oxalobacter formigenes*, which is a commensal anaerobe that uses only oxalate as its sole carbon source (19,20). Investigations in a number of laboratories including ours, have confirmed that colonizing rats with *Oxalobacter* is consistently effective in reducing urinary oxalate excretion (21,22). A potential role for these bacteria in contributing to oxalate homeostasis is a reduction in the

intraluminal oxalate load available for absorption across the intestine because of this oxalate-degrading action. In the mid-nineties, we provocatively proposed that, because of its substrate specificity, *Oxalobacter* may have a dual action of deriving oxalate from systemic sources, possibly deriving blood sources of its substrate by promoting enteric excretion of oxalate, in addition to intraluminal degradation. It is noteworthy that a compensatory pathway for enteric oxalate excretion was already documented by us and reported to occur in rats when renal function is compromised and this was attributed to activation of an angiotensin II (Ang II) signaling pathway in the large intestine (23,24). Subsequently, *Oxalobacter*-induced enteric oxalate excretion was confirmed for the first time in our laboratory using rats (21) and, in later studies, using mice (25,26). Notably, we have since determined that this *Oxalobacter*-induced enteric oxalate excretion is not mediated via Ang II since net oxalate secretion across colonized tissues was unaffected by the acute *in vitro* application of the specific Ang II receptor (AT1) antagonist, losartan, to the serosal bathing solution. The earlier study in rats (21) provided compelling evidence that the bacteria may produce a soluble secretagogue that initiates the enteric excretion of oxalate since oral administration of encapsulated bacterial lysate (cell membrane-free preparation) to rats produced changes in intestinal oxalate movements comparable to *Oxalobacter* colonization leading to reductions in urinary excretion. However, the precise signaling molecules and pathways involved in this physiological bacteria-host interaction have yet to be elucidated.

Remarkably, colonization of a mouse model [the alanine-glyoxylate aminotransferase (AGT) knockout] of the genetic disease Primary Hyperoxaluria, type 1 (PH1) with OXWR (a wild rat strain of *Oxalobacter*) resulted in a normalization of the hyperoxaluria and hyperoxalemia exhibited in non-colonized counterparts (26). This modulation of transmural oxalate transport was attributed to a physiological interaction between the bacteria and the enterocyte which promoted active transmural net oxalate secretion across the caecum and distal colon. Subsequent studies confirmed that the human *Oxalobacter* strain, HC-1, produced similar results in both the small and large intestine of wild type mice (25). Reductions in 24-h urinary oxalate excretion exceeding 90%, via the development of robust OXWR colonization, in mice are evident through time confirming the superior efficiency and efficacy of *Oxalobacter formigenes* in promoting enteric excretion and in degrading intraluminal oxalate (26).

Bifidobacterium sp.

The modulation of intestinal oxalate transport by *Oxalobacter* prompted a study examining the effects of oxalate-degrading *Bifidobacterium animalis* compared to the non-degrader *Bifidobacterium adolescentis* since a 44% and 33% reduction in urinary excretion of oxalate in C57Bl/6 wild type and AGT knockout mice, respectively, was confirmed with *B. animalis* (27). The results showed that, in contrast to *Oxalobacter sp.*, colonization of mice with *Bifidobacterium sp.* did not affect intestinal oxalate flux (27). Consequently, it was concluded that intraluminal oxalate degradation by *B. animalis* led to a reduction of the amount of oxalate available for absorption and lowered urinary oxalate. We subsequently sought to examine whether combined administration of HC-1 and *B. animalis* to mice would have a synergistic effect in reducing urinary oxalate excretion in AGT knockout mice. The protocol implemented in this study design was as previously described (25) except the gavage inoculum contained both HC-1 and *B. animalis* for one of the mouse groups and HC-1 alone for the other (n=6 in each group). Twelve days following the gavage procedure when mice were confirmed colonized, urine was collected for 24 h and the mice were then euthanized and oxalate fluxes were measured across the distal ileum, caecum, and distal colon. Compared to baseline values, urinary oxalate was found to be lower by 56% in the HC-1 treated animals compared to a 40% reduction in the group that received the combined inoculum (*Figure 1*). The flux results were surprising and revealed that the magnitude of net oxalate secretion promoted by HC-1 in all intestinal segments was attenuated somewhat when *B. animalis* was delivered in the combined inoculum (*Figure 2*). The magnitude of the net flux trended lower in all segments examined but reached significance only in the caecum due to a reduction in J_{sm}^{Ox}. As shown in *Table 1*, there were no changes in the associated electrical parameters of the tissue segments removed from both groups. This attenuated response in enteric oxalate excretion is reflected by the 16% higher urinary oxalate excretion in the mice that received the combined inoculum compared to HC-1 alone. A definitive explanation for this unexpected result is not readily available and warrants further study. It may be that competition for substrate, or indeed the establishment of a niche between both oxalate-degraders, are in play here. Given that *B. animalis* is a generalist oxalotroph, this versatile feature may endow some competitive advantage to this bacterial species over *Oxalobacter* in mouse intestine *in vivo*.

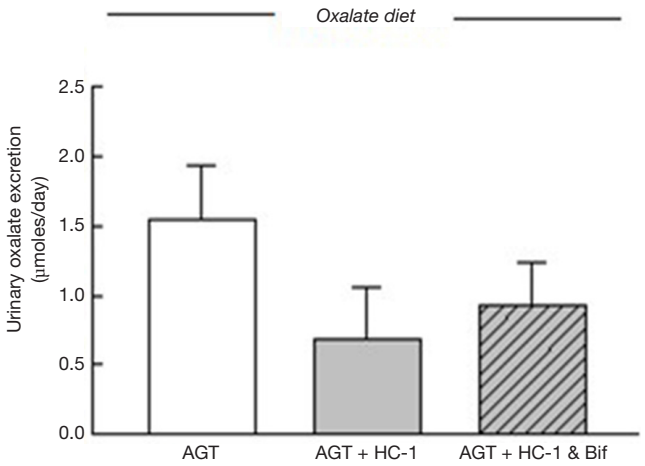

Figure 1 Comparison of 24-h urinary oxalate excretion in AGT knockout mice before (n=12) and 12 days after oral gavage with either HC-1 alone (n=6) or a combined inoculum of HC-1 and *B. animalis* (n=6). These mice were being fed a diet supplemented with 1.5% oxalate during the study period. Reductions in urinary excretion did not reach a level of significance using an ANOVA: P≤0.05.

Lactobacillus sp.

More recently, we compared the effects of colonizing C57Bl/6 mice with two oxalate-degrading strains of *Lactobacillus sp.* on urinary oxalate excretion and intestinal oxalate transport in a similar study design as described for *Bifidobacterium* (27). The oxalate-degrading activity of the two *Lactobacillus* strains was previously documented (28) and confirmed in our hands prior to initiating the experimental design. The results of this study revealed that both *L. acidophilus* and *L. gasseri* comparably reduced 24-h urinary oxalate by 34% (from 1.1±0.3 to 0.7±0.1 µmoles/24 h, n=7) and 32% (from 1.4±0.2 to 0.9±0.3 µmoles/24 h, n=6), respectively. The flux studies examining oxalate movements across the distal colon (shown in *Figure 3*), caecum, and d-ileum (results not shown) removed from these mice exhibited no changes when compared to contemporary controls that were not administered either *Lactobacillus* strain. In addition, there were no changes in the associated electrical parameters of the tissue segments removed from the three animal

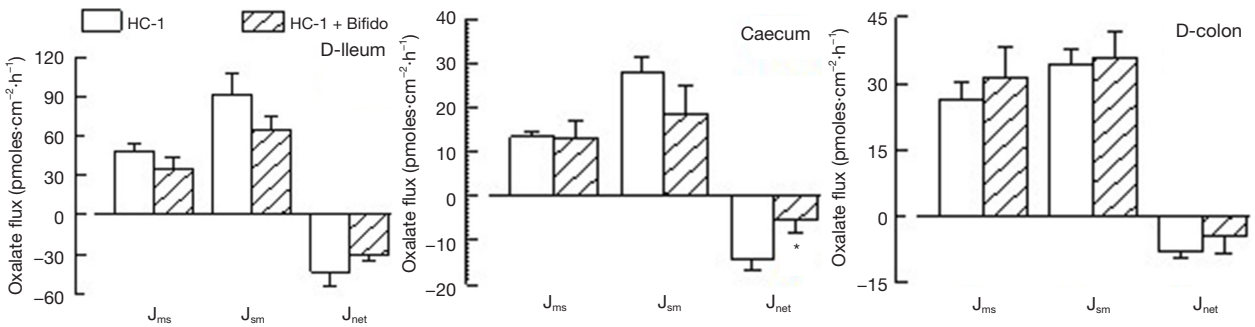

Figure 2 Unidirectional fluxes of oxalate (J, pmoles·cm^{-2}·h^{-1}) measured across the isolated, short-circuited distal ileum, caecum, and distal colon removed from AGT knockout mice either colonized with HC-1 alone or with a combined inoculum of HC-1 and *B. animalis* (n=6 tissue pairs in each group) fed a diet supplemented with 1.5% oxalate for 12 days. Transepithelial conductance (G_T) and short circuit current (I_{sc}) were not statistically different between the two animal groups (see *Table 1*). D-lleum, distal ileum; D-colon, distal colon.

Table 1 Transepithelial conductances and short-circuit currents recorded from intestinal tissues of two groups of AGT knockout mice colonized with either HC-1 alone or with a combined inoculum of HC-1 and *B. animalis* (n=12 tissues in each group)

Segment parameter	Distal ileum I_{sc}	G_T	Caecum I_{sc}	G_T	Distal colon I_{sc}	G_T
HC-1	−6.2±1.4	34.7±1.9	−1.2±0.6	21.8±1.6	−1.9±0.5	16.2±1.3
HC-1 + *B. animalis*	−5.4±0.7	33.6±1.6	−1.3±0.4	18.2±0.9	−1.9±0.2	18.9±1.7

Values are mean ± SEM. No statistical differences between groups were determined employing an unpaired *t*-test: P≤0.05. G_T, transepithelial conductance (mS/cm^2); I_{sc}, short-circuit current (µEq.cm^2.h).

groups (see *Table 2*). Thus, it was concluded that this effect of lowering urinary oxalate occurred as a consequence of a reduction in the availability of oxalate because of intraluminal oxalate degradation. Consequently, it appears that amongst the three oxalate-degrading bacterial species examined, *Oxalobacter sp.* is unique in modulating the intestinal transport of its sole carbon source which clearly has significant relevance from an evolutionary biology perspective.

Probiotic oxalate-degrading bacteria in humans

In contrast to the studies in experimental animals, proof that these intestinal bacteria have a physiologically relevant role in contributing to oxalate homeostasis in humans has been more difficult to substantiate (14,17,29-38). This is discussed in a contemporary review (13) by this author emphasizing that "potential reasons for the conflicting and sometimes transient probiotic effects may include a lack of standardization of the various bacterial formulae and poor dietary control of oxalate and calcium intake in the experimental study design". However, given the backdrop of reports showing human patients forming oxalate kidney stones, who are *Oxalobacter*-negative, have significantly higher plasma (37) and urinary oxalate excretion (37,39-42) and recurrent kidney stone episodes appear to correlate with the lack of *Oxalobacter* colonization (22,37,43,44), more rigorous design and implementation of human patient studies are required in order to reconcile the apparent beneficial probiotic affects in experimental animals compared to the conflicting and inconsistent results from studies in humans.

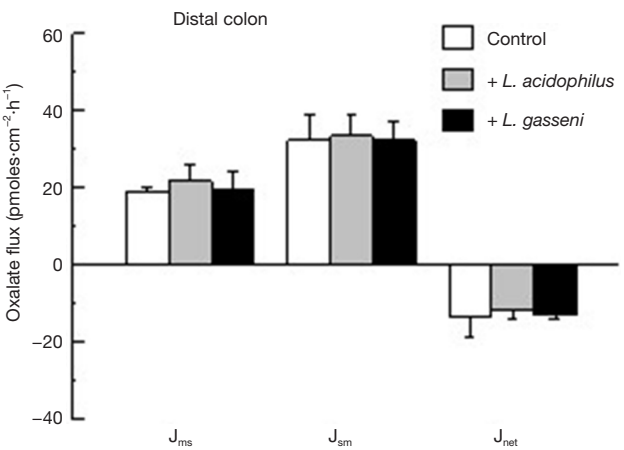

Figure 3 Unidirectional fluxes of oxalate (J, pmoles·cm^{-2}·h^{-1}) measured across the isolated, short-circuited distal colon removed from C57BL/6 wild type mice colonized with *L. acidophilus*, or *L. gasseri*, compared to control mice not colonized (n=6 in each group) and fed a diet supplemented with 1.5% oxalate for 12 days. Transepithelial conductance (G_T) and short circuit current (I_{sc}) recordings were not statistically different among the three animal groups (see *Table 2*).

Oxalobacter colonization

Two studies that determined the prevalence of *Oxalobacter* colonization in the American population reported an overall prevalence of 38% in 247 adults between 18 and 69 years old (45) and 31% in 242 younger adults aged between 18 and 40 years (46) and it was noted that antibiotic consumption is a major factor impacting colonization status (45). In fact, very little is known about any of the factors that foster or repress the persistence of *Oxalobacter* colonization in humans or in experimental animals other than the sensitivity to certain antibiotics (47-49). Thus, there is a large gap in information and a lack of knowledge regarding this important aspect particularly in light of potential probiotic formulae under development. In laboratory animals, it has been generally acknowledged that, compared to their wild animal counterparts and due to breeding in specific pathogen-free (SPF) environments, these experimental models are not naturally colonized.

Table 2 Transepithelial conductances and short-circuit currents recorded from intestinal tissues of three groups of C57Bl/6 wild type mice colonized with either *L. acidophilus* or with *L. gasseri* compared to control mice not colonized (n=12 tissues in each group)

Segment parameter	Distal ileum I_{sc}	G_T	Caecum I_{sc}	G_T	Distal colon I_{sc}	G_T
Control	–9.7±1.1	38.2±3.2	–3.6±0.2	20.8±2.9	–2.2±0.3	14.4±0.9
L. acidophilus	–8.2±1.3	39.6±3.5	–3.7±0.7	22.0±1.7	–2.3±0.4	14.9±1.3
L. gasseri	–8.2±1.3	37.5±3.8	–2.9±0.3	21.7±2.1	–2.3±0.3	13.2±1.2

Values are mean ± SEM. No statistical differences between groups were determined employing an ANOVA: P≤0.05. G_T, transepithelial conductance (mS/cm^2), I_{sc}, short-circuit current (μEq.cm^2.h).

However, our routine laboratory protocol tests every animal for the presence of *Oxalobacter* upon arrival into our animal holding facility and on two occasions, within the past 3 years, several C57BL/6 mice purchased from a well-known vendor were found to be colonized with *Oxalobacter* [detected by fresh fecal sample collection and inoculation into anaerobic media selective for oxalate-degrading activity (26) within 2 hours of receiving the mice into our mouse facility]. These fecal specimens were submitted for genomic sequencing at the University of Florida Core Services and results from the testing (qPCR of formyl-CoA transferase gene and sequencing 16S rRNA) confirmed that the oxalate-degrading bacteria were *Oxalobacter*. Another similar case was reported in 1987 by Daniel *et al*. who purchased rats from another vendor that were found to harbor oxalate-degrading bacteria (50). This underscores the importance of determining the *Oxalobacter* status of commercially available rodents prior to implementing experimental protocols on gut microbiota and oxalate homeostasis.

Another debatable aspect that we sought to address is the requirement to "prime" experimental rodents with an oxalate-supplemented diet prior to artificially colonizing the animals by an esophageal gavage with an *Oxalobacter* inoculum (26,51). Most investigators, including ourselves (21,25,26,52,53), have fed a "priming" diet since laboratory rodent chow appears to contain a nominal oxalate content. Support for feeding an oxalate priming diet prior to artificially colonizing rats was provided by Allison *et al.* who reported that the "*establishment of a population of Oxalobacter in adult rats (that were not previously colonized) did not occur unless a relatively high level of sodium oxalate (3% or more) was added to the diet*" (50,51). Further, Sidhu *et al.* reported that artificially colonized rats lose colonization within 5 days if dietary oxalate supplementation is stopped (54). We re-examined this supposition in mice by conducting a simple study involving 12 C57BL/6 mice. The mice, which were determined not to harbor *Oxalobacter* prior to study, were randomly divided into two groups, n=6 in each. One group was "primed' by administering an oxalate-supplemented diet [1.5% (26)] for 5 days while the other was fed regular chow (Harlan Teklad #7912). Both groups were orally gavaged using the same HC-1 inoculum and protocol as previously described (26) and fresh fecal material was collected directly from all mice once a week for 77 days and inoculated into anaerobic media containing 20 mm oxalate for detection of oxalate-degrading activity (26). The oxalate-supplemented diet was replaced by regular chow in the "primed" group 12 days after the colonization procedure and both groups were fed the same rodent chow for the remainder of the study period. The results revealed unequivocally that at the end of the study period 100% of mice in both groups were found to be *Oxalobacter*-positive indicating that the provision of an oxalate-supplemented diet was not necessary for successful colonization of mice with *Oxalobacter*.

Clearly, the bioavailability of luminal oxalate will be a major factor in sustaining *Oxalobacter* colonization since this is the sole carbon source of these bacteria and we have shown that *Oxalobacter* can derive oxalate from systemic sources (21,25,26). However, other factors such as intraluminal calcium play an important role in so far as this ion impacts oxalate bioavailability by complexing with oxalate and forming the highly insoluble salt. In studies using rats, we have provided results showing that "the maintenance of *Oxalobacter* colonization appears to be exquisitely sensitive to the balance between intraluminal calcium and oxalate availability" (21). Also, in small study conducted in human individuals on controlled diets, Jiang *et al.* showed the impact of elevating intraluminal calcium 5-fold which resulted in reducing the number of fecal *Oxalobacter* by 5-fold (30). Conversely, the same study reported that increasing dietary oxalate 15-fold facilitated a 12-fold increase in fecal *Oxalobacter* (30). An interesting study on wild white-throated woodrats (*Neotoma albigula*) also reported that the impact of increasing dietary oxalate promotes complex interactions in the gut microbiome to include a beneficial effect on a community of bacteria involved directly/indirectly in luminal oxalate degradation. These physiologically relevant interactions within the gut microbiota certainly warrant further study in addition to studies on host-microbiota interactions in order to elucidate, as yet unknown, additional factors that impact *Oxalobacte*r colonization.

Intestinal colonization of *Oxalobacter* is clearly affected by other unknown factors that are independent of luminal bioavailability of oxalate or intraluminal calcium (26) as we have found in studying the AGT knockout mouse model. This was evident in a study that compared artificially and naturally colonized AGT knockout mice administered diets with varying calcium content with/without oxalate (26). In every group of AGT knockout mice, colonization was lost within 3–4 weeks compared to the retention of colonization in the control group (26). The results of several small studies of PH1 patients administered *Oxalobacter* generally showed transient reductions in urinary oxalate excretion that were reversed when probiotic treatment was terminated

suggesting colonization was not achieved by the treatment (29,33,34). Whether these patients have an inherently hostile intraluminal environment with respect to *Oxalobacter* colonization, similar to what is observed in the animal model of this genetic disease, is purely speculative but warrants study since this patient group, in particular, would benefit greatly from a probiotic therapeutic approach.

Another learning opportunity regarding intestinal *Oxalobacter* colonization is presented by examining the heterogeneity of the different intestinal segments that support the presence of *Oxalobacter* for varying periods of time (25). A study conducted by us in wild type mice showed that *Oxalobacter* can transiently reside in the small intestine, specifically in the proximal jejunum, mid- and distal-ileum in some mice. In contrast, sustained colonization was observed in all mice in the large intestine. Given the large variations in pH as well as in the general chemical milieu and composition of the microbiome of each of these segments, addressing these questions presents a complex and challenging task. Add to this, the heterogeneity of the segment specific oxalate transport proteins sub-serving the basal characteristics of oxalate movements in each segment and numerous other questions arise. Among the most basic of questions, however, is the physical location of *Oxalobacter* with respect to the apical surface of the enterocyte? Where in that microenvironment does *Oxalobacte*r reside and what are the microenvironmental factors that impact retention of this oxalotrophic specialist? If the mechanism whereby *Oxalobacter* modifies epithelial oxalate transport is via the elaboration of a secretagogue as previously proposed (21), the nature of the microclimate and distance influencing the diffusion of this purported secretagogue is relevant information.

A final consideration affecting *Oxalobacter* colonization is the destabilization of the intestinal microbiome with the introduction of different feeds and new environments. This is not a trivial issue as we have experienced upon moving our experimental mice from an older facility to a newly built facility at our institution some years ago. This seldom acknowledged factor was elegantly addressed experimentally by Ussar *et al.* who demonstrated that "*the composition of microbiota is highly dependent on diet*, *environmental history*, *and host genetics*" (55) due to remodeling of gut microbiota. This presents a quagmire when trying to reconcile inconsistencies in results within and between different laboratories and underscores the importance of each investigative laboratory to normalize their experimental animals with respect to these factors.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: All applicable international, national, and institutional guidelines for the care and use of animals in the studies included in this report were followed. This article does not contain any studies with human participants performed by the author.

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