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Prebiotics and synbiotics: Dietary strategies for improving gut health

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Prebiotics and synbiotics: Dietary strategies for improving gut health

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Purpose of review — A wide range of dietary carbohydrates, including prebiotic food ingredients, fermentable fibers, and milk oligosaccharides, are able to produce significant changes in the intestinal microbiota. These shifts in the microbial community are often characterized by increased levels of bifidobacteria and lactobacilli. More recent studies have revealed that species of *Faecalibacterium*, *Akkermansia*, and other less well studied members may also be enriched. We review the implications of these recent studies on future design of prebiotics and synbiotics to promote gastrointestinal health.
Recent findings — Investigations assessing the clinical outcomes associated with dietary modification of the gut microbiota have shown systemic as well as specific health benefits. Both prebiotic oligosaccharides comprised of a linear arrangement of simple sugars, as well as fiber-rich foods containing complex carbohydrates, have been used in these trials. However, individual variability and nonresponding study participants can make the outcome of dietary interventions less predictable. In contrast, synergistic synbiotics containing prebiotics that specifically stimulate a cognate probiotic provide additional options for personalized gut therapies.
Summary — This review describes recent research on how prebiotics and fermentable fibers can influence the gut microbiota and result in improvements to human health.

Keywords: fiber, gut microbiota, oligosaccharides, prebiotics, probiotics, synbiotics

Introduction

Despite the considerable research attention recently devoted to diet and microbiota, the notion that dietary components can influence gastrointestinal microbiota composition and enhance host health is not new. Indeed, this very hypothesis was envisioned more than a century ago, long before any specific foods or food constituents had been identified and before techniques for assessing microbiota complexity could be appreciated [1,2]. One of the first specific dietary components to be recognized for its unique impact on the gut microbiota was breast milk [3]. Eventually, the prebiotic concept was introduced to describe those food ingredients or constituents that enrich for beneficial organisms in the gastrointestinal tract (GIT) [4]. In the past two decades, appreciable experimental and clinical evidence has emerged suggesting that prebiotics may promote gastroenterological homeostasis and/or redress specific disease states associated with microbial imbalance (i.e., dysbiosis) [5*].

Like prebiotics, probiotics have also long been used as therapeutic agents for improving gastrointestinal health. However, most probiotic microorganisms are allochthonous to the intestinal environment and are generally unable to colonize or persist in the GIT [6,7]. Prebiotics have a decided advantage by enriching for organisms already present in the gut ecosystem (so-called autochthonous members). Fermentation of prebiotic carbohydrates yields butyrate and other short chain fatty acids, as well as other end products that lower the local pH, stimulate mucin

Key Points

- The human gut microbiota is profoundly influenced by prebiotic food ingredients as well as fermentable fibers and oligosaccharides found in human milk.
- Shifts in the gut microbiota are associated with positive systemic as well as specific health outcomes although clinical data are equivocal, in part because some individuals do not respond to prebiotic treatments.
- Dietary strategies based on mixtures of prebiotic fibers or rationally designed synbiotic approaches may be more effective at modulating the gut microbiota.

Table 1. Simple and complex prebiotics

Simple	Complex
Inulin	Pectins
Fructooligosaccharide	Human milk oligosaccharide
Galactooligosaccharide	Resistant starch
Isomaltooligosaccharide	Arabinoxylan
Mannan oligosaccharide	

Adapted from [22].

production by colonocytes, and induce production of immunomodulatory cytokines [8]. Thus, prebiotics not only cause shifts in the microbiota by supporting growth of particular GIT members but also serve as substrates for production of biologically active metabolites.

Prebiotics now provide food formulators, as well as clinicians, with rather simple diet-based opportunities to influence the composition of the gut microbiota and improve intestinal health. In this review, we describe current strategies for how prebiotic approaches can be used to achieve these goals. Specifically, we address the prebiotic activity of fiber-rich foods, why some individuals respond to prebiotics and others do not, and the advantages of rational or synergistic synbiotics for inducing beneficial shifts in the gastrointestinal microbiota.

Prebiotics in 2016: Emerging Concepts

Despite the substantial industrial and clinical interest in prebiotics, the commercial market has been dominated by only a handful of prebiotics, mainly inulin, fructooligosaccharides, and galactooligosaccharides (GOS) [9,10]. Several isomaltooligosaccharides products are also commercially available [11]. In the United States, European Union, and Pacific Rim, these prebiotics are added as functional ingredients in a wide variety of processed foods and beverages. Infant formula products, in particular, are often supplemented with GOS or fructooligosaccharides because of their ability to mimic a bifidogenic response similar to that which occurs with human milk oligosaccharides in breast-fed infants [12,13].

Also documented to have prebiotic activity are resistant starches, starches that are resistant or slowly resistant to digestion and reach the colon intact. Depending on the type of resistant starches, studies have shown they enhance growth of bifidobacteria, as well as *Eubacterium rectale*, *Ruminococcus bromii*, and lactobacilli [5*,14–17]. Some of these changes in the microbiota are correlated with glycemic improvements [18] and high butyrate production [19]. The latter could be favorable for the prevention of colon cancer and inflammation [20,21]. In general, these commercial prebiotics consist of mostly linear oligosaccharides or polysaccharides that contain only one or two monomeric sugars (Table 1) [22].

There is also considerable evidence showing that several dietary fibers have prebiotic activity [23*]. In contrast to the rather simple, linear composition of commercial prebiotics, the carbohydrates in plants as well as those present in human milk (Table 1) are diverse and structurally complex, with many containing functional groups [13,24*,25]. In the gut, they require participation of a more extensive and diverse array of hydrolytic enzymes to degrade these molecules into fermentable substrates [24*,26**]. Accordingly, there may be different host-dependent responses, as the specific form or type of dietary fiber consumed by an individual may differentially affect the response of the microbiota [26**,27].

Prebiotic fibers are often natural constituents of a variety of foods, especially whole grains, fruits, root and other vegetables, and legumes. Although some foods contain appreciable concentrations of these prebiotics [28], in most western diets, consumption of these fiber-rich foods is probably too low to contribute much fermentable fiber to the colon. However, for individuals who consume whole grain products and fiber-rich diets, significant effects on the microbiota have been observed, with shifts in the abundance of specific taxa and increased microbial diversity [18,23*,29]. In contrast, other studies have shown that whole grain consumption does not always induce changes in gut microbiota [30] or consistently affect clinical end points [31].

Based on these observations, several researchers have suggested that prebiotics are best defined based on their

physiological effects or functional capacities rather than the specific microbial targets affected [32*,33]. So-called second generation prebiotics were envisioned as providing specific functional benefits. According to this argument, dietary fibers may have prebiotic activity by causing broad changes in community structure, but without necessarily influencing abundances of bifidobacteria or lactobacilli [34].

It is worth noting that the convergence of "prebiotics" and "fiber" has led to the development of a new lexicon in the prebiotic community [35]. Indeed, "low-digestible" [36] and "nondigestible carbohydrates" [37], "prebiotic fiber" [34], "functional fiber", and "fermentable fiber" [38] are among the terms used to describe the food carbohydrates that have microbiome-influencing properties. Neither is there consensus on definitions of prebiotics nor the specific types of fiber [38,39]. Recently, Sonnenburg and Sonnenburg [40**] introduced the term "microbiota- accessible carbohydrate" (MAC) to describe fibers, as well as host-secreted mucin and microbial-produced saccharides, that are available as substrates for the gut community. The absence of these fibers in the colon (as a result of low-fiber diets) may result in gut microbes looking elsewhere for sugars, namely, the mucin layer that protects the host.

Prebiotics, the Healthy Gut Microbiota, and the Challenge of Individual Variation

Although several microbial taxa or genera have been suggested as being beneficial to the host (i.e., *Bifidobacterium* and *Lactobacillus* spp. [41,42]), there is still no actual definition of what constitutes a healthy gut microbiota [32*,43]. One recent study showed that gut microbiota from healthy human hunter gatherers was significantly different from a healthy western cohort, suggesting that the ideal or optimal composition of an individual's gut microbiota depends on the lifestyle of the individual [44]. Although enrichment of specific taxa by diet is possible, the clinical significance of these changes may not be readily apparent. Indeed, organisms not previously recognized as contributing to host heath, including *Eubacteria, Faecalibacter, Akkermansia, Ruminococcus*, and *Roseburia*, are known to respond to prebiotics [5*,16,45,46*]. Finally, several microorganisms categorized previously as detrimental are now recognized as part of the gut "normobiosis" and may even be beneficial. For example, Clostridia spp. have recently been shown to be beneficial in the attenuation of diseases in models of colitis and allergic diarrhea [42,47,48].

Significant interindividual variability [49] can also make the outcome of dietary interventions less predictable. Indeed, multiple studies have reported the occurrence of study participants who respond to prebiotics and other dietary treatments (responders), whereas in similar studies, study participants fail to respond (nonresponders) to the same treatments [14,43,50,51]. Responses to dietary interventions likely depend on the taxonomic and functional composition of the gut microbiota. Thus, when a given compound is selectively fermented by a limited number of bacteria (fulfilling the actual definition of prebiotic) the response will depend on the gene content and functionality of the target bacteria before supplementation. The presence of species known to metabolize certain compounds, however, is not a guarantee of a positive response to prebiotic supplementation. For instance, dietary interventions in obese study participants resulted in decreased cholesterol concentrations, but only in individuals with high initial levels of *Clostridium sphenoides* [43]. Furthermore, Davis *et al.* [52] showed that a fraction of study participants who had consumed as much as 10 g GOS/day for 3 weeks did not respond to the treatment, even though they harbored bifidobacteria at similar levels as that of responders. The authors suggested that nonresponders may lack specific strains capable of metabolizing GOS [52].

The ability of a particular species to ferment certain prebiotics is strain specific [53–55]. Thus, GIT environments having a similar taxonomic assembly might differ in functional capabilities and therefore result in different responses to prebiotics interventions. Moreover, although a given strain may have the biochemical and physiological means to transport and metabolize a prebiotic, it must also outcompete other autochthonous members of the microbiota to actually utilize the prebiotic compounds and potentially expand its population [52]. Ultimately, the complexity and individuality of the gut microbiota and the structural complexity of dietary fibers likely contribute to the phenomenon of responders and nonresponders.

As a practical strategy, consumption of fermentable fiber or combinations of prebiotics may enrich for a larger and more diverse population of gut microbes. This strategy could potentially reduce the occurrence of nonresponders. In addition, stimulating a broader spectrum of microorganisms, either directly or via cross-feeding, could also promote greater diversity within the gut ecosystem. High levels of diversity are generally considered important for a functional gut ecosystem [56]. Several human gastrointestinal diseases are associated with reduced microbial diversity and gene richness [5*]. In particular, reductions in Firmicutes are frequently described [57]. Reduced diversity has also been reported to have an impact on the production of beneficial metabolites by gut microbes. For example, antibiotic treatments and diarrheal disease are characterized by reduced or altered

production of short chain fatty acids [58,59]. In contrast, increased diversity has been associated with an improvement in insulin sensitivity [60]. Furthermore, and perhaps most importantly, the restoration of a diverse gut microbiota is associated with successful treatments for *C. difficile* infections [61*].

Ultimately, the success of a prebiotic treatment depends on its ability to enhance health or reduce a disease phenotype. Several meta-analyses and systematic reviews of human trials with various prebiotics have been conducted with various end points assessed (Table 2) [62–71]. In general, these analyses have shown that commercial prebiotics were effective for some conditions (i.e., constipation and diarrhea), but not others (i.e., cholesterol reduction and eczema).

Synbiotics to the Rescue

Although some attempts to predict responses to dietary interventions based on the microbial composition of the gut prior to prebiotic consumption [43] have proven successful, it remains a challenge for practitioners and dietitians to recommend specific prebiotics to patients because of highly individualized responses. Accordingly, when rationally formulated, synbiotics may provide an effective strategy to enhance persistence and metabolic activity of specific beneficial probiotic strains. The most commonly used synbiotic combinations contain lactobacilli and bifidobacteria, as the probiotic component, and oligosaccharides, inulin, or fibers as the prebiotic component [72]. Despite the potential advantages of these products, however, how these synbiotics are specifically formulated can have considerable influence on their potential effectiveness.

When the synbiotic concept was first introduced [4], two configurations were proposed. Either the prebiotic and probiotic components are chosen independently of one another, with each responsible for a particular effect or health benefit (complementary synbiotics); or the synbiotic combination is specifically designed with a prebiotic substrate synergistically supporting the competitiveness, survival, or metabolic activity of a cognate probiotic strain in the gastrointestinal ecosystem (synergistic synbiotics) [73]. These synergistic synbiotics have the potential advantage of functioning even in prebiotic nonresponders, since they would not require the presence of responder strains. Furthermore, the incorporation of a selective fermentable substrate represents a resource opportunity that increases the competitive fitness of the partner organism and could enhance its persistence [74].

Although several meta-analyses of synbiotic trials suggest clinical benefits (Table 3) [62,71,75–77], most trials have lacked experimental power or were designed such that the treatment effects could not be determined, that is, the treatment effects of the pro and prebiotic were not determined independently. Additionally, microbial analyses either were absent in several studies or the analytical methods were conducted at higher taxonomical levels and were not strain specific. Thus, only very few studies showed that the synbiotic had functioned synergistically *in vivo* [78,79,80*,81,82]; only one of these studies was conducted in humans [82].

As noted above, for most synbiotic products, selection of pro and prebiotic pairs has been based on arbitrary considerations [80*] rather than on rational selection of synbiotic constituents. Although in-vitro screenings of potential synbiotic combinations are routinely used, such approaches do not account for ecological efficacy or effectiveness [83–88]. Moreover, in-situ predictions for how an individual will respond to prebiotics based on genome content may also be limited, in part, because they do not account for competitiveness and other interactions with autochthonous members of the gut microbiota (i.e., cross-feeding and predation) [52,89,90]. Nonetheless, such analyses can be a valuable first step toward designing synergistic synbiotics.

Recently, two novel approaches, both based on ecological performance or fitness, have been proposed for developing synergistic synbiotics. The in-vivo selection method relies on the selection and isolation of strains whose abundance is significantly enriched in study participants who had consumed a given prebiotic [80*]. When recombined as a synbiotic and introduced into a new host, these strains would be expected to colonize at greater levels than in the absence of the prebiotic. This approach was recently tested in an animal model. The synbiotic consisted of a strain of *B. adolescentis* (IVS-1) that had been enriched by GOS in a single human study participants [52]. When combined with GOS and fed to rats, the abundance of *B. adolescentis* increased to about 30% of the total population [80*].

The other approach, called multitaxon INsertion Sequencing, uses libraries of transposon mutants of bacterial strains with probiotic interest to identify genes that determine the fitness of that bacteria in response to a prebiotic treatment [91*]. Not only are bacteria that are specifically responsive to the treatment recognized *in vivo* but also the genes that drive the response are identified. As the authors state, however, this promising technique currently cannot distinguish between primary effects induced by the diet and secondary community driven, ecological effects.

Table 2. Overview of meta-analyses on prebiotics

Author/year	Disease phenotype	Studies and study participants included	P value	Type of prebiotic	Study participants	Outcome
Beserra et al. (2015) [62]	Total cholesterol	9 trials (*n*=313)	0.314	FOS, GOS, inulin, or oligofructose	Overweight or obese adults	No significant reduction in total cholesterol
		9 trials (*n*=278)	0.496			No significant reduction in LDL-c levels.
		9 trials (*n*=278)	0.621			No significant reduction in fasting glucose
		8 trials (*n*=219)	0.081			Significant reduction in fasting insulin
		10 trials (*n*=313)	0.438			Prebiotic tends to increase HDL-c
		10 trials (*n*=313)	0.156			No significant reduction in triglyceride levels
Lohner et al. (2014) [63]	Acute infectious diseases	2 trials (*n*=715)	0.34	Oligofructose, GOS/FOS	Infants and children	Reduced febrile episodes
		3 trials (*n*=671)	<0.00001	(sc)GOS, (lc)FOS, oligofructose		Reduced antibiotic treatment
		3 trials (*n*=747)	0.34	Oligofructose, GOS/FOS		Reduced diarrheal episodes
Zaman et al. (2015) [64]	Diarrhea in patients receiving EN	6 trials (*n*=354)	0.77		EN patients, critically ill	Reduced diarrhea in critically ill patients
		8 trials (*n*=568)	<0.00001	Fiber	EN patients, not critically ill	Reduced diarrhea in not critically ill patients
		3 trials (*n*=157)	0.81	Prebiotics	EN patients	Effect is inconclusive
Kellow et al. (2014) [65]	Metabolic health	5 trials (*n*=52)	<0.05	Oligofructose, chicory-derived fructan	Healthy adults	Satiety is promoted
		5 trials (*n*=208)	0.16	Oligofructose, inulin, ALA, FOS	Overweight patients or type II diabetes	Satiety is not promoted
		4 trials (*n*=131)	<0.05	Oligofructose, chicory-derived fructan, FOS, inulin	Normal-weight and obese patients	Reduced postprandial glucose concentrations
		3 trials (*n*=121)	<0.05	Oligofructose, inulin, FOS	Normal-weight, overweight and obese patients	Reduced postprandial insulin concentrations

Author/year	Disease phenotype	Studies and study participants included	P value	Type of prebiotic	Study participants	Outcome
Chiavaroli et al. (2014) [66]	Chronic kidney disease	13 trials (*n*=150)	0.006	Inulin, fermentable fibers, arabinogalactan, gum, lactulose, high- vs. low-fiber foods	Patients with chronic kidney disease or on hemodialysis	Fiber reduces serum urea
		12 trials (*n*=117)	0.02			Fiber reduces serum creatinine
		7 trials (*n*=72)	0.47	Inulin, fiber, lactulose, wheat bran, high-fiber foods		Fiber has no effect on serum phosphorus
Collado Yurrita et al. (2014) [67]	Bowel function	5 trials (*n*=144)	NG	Inulin	Adults with chronic constipation	Improved stool frequency
		2 trials (*n*=96)				Improved stool consistency
		2 trials (*n*=80)				Improved food transit time
		2 trials (*n*=80)				Improved stool hardness
		2 trials (*n*=80)				No improvement for pain and bloating
Moayyedi et al. (2014) [68]	IBS	15 trials (*n*=590)	0.0005	Bran, ispaghula, linseeds, fiber (unspecified)	Patients with IBS	Fiber has a significant benefit for treating IBS
		6 trials (*n*=441)	0.14			Bran has no benefit in IBS treatment
Srinivasjois et al. (2013) [69]	NEC	5 trials (*n*=345)	NG	scGOS+lcFOS; lactulose		Supplementation was safe, no decreased incidence of NEC or late onset sepsis
	Late onset sepsis	3 trials (*n*=295)	0.23	scGOS+lcFOS; lactulose		
Dang et al. (2013) [70]	Development of eczema	3 trials (*n*=510)	>0.05	scGOS+lcFOS+pAOS; scGOS+lcFOS; PDX+GOS+LOS	Infants (1–2 years; 4 months)	No significant effects of prebiotic consumption on development of eczema in infants. No consistent changes for sensitization
Shukla et al. (2011) [71]	MHE	5 trials (*n*=117)	<0.0001	Lactulose	Adults	Significant reduction of risk of no improvement of MHE with no intertrial heterogeneity

EN, enteral nutrition; FOS, fructooligosaccharides; GOS, galactooligosaccharides; IBS, irritable bowel syndrome; lc, long chain; MHE, minimal hepatic encephalopathy; NEC, necrotizing enterocolitis; NG, not given, Sc, short chain.

Table 3. Overview of meta-analyses on synbiotics

Author/year	Disease phenotype	Studies and study participants	P value	Type of synbiotic	Study participants	Outcome
Shukla et al. (2011) [71]	HE	1 trial (*n*=55)	0.004	Probiotic: PP, LM, LPSP, LP2; prebiotic: BG, I, P, RS	HE patients	Synbiotic use reduced the risk of no improvement of minimal hepatic encephalopathy
		1 trial (*n*=60)		Probiotic: BL; prebiotic: FOS, vitamins B1, B2, B6, B12		
Ford et al. (2014) [75]	IBS and chroic idiopathic constipation	2 trials (*n*=198)	0.09	Probiotic: BL, BB, LR, LA, LB, ST,LC; prebiotic: FOS	IBS patients	No reduced symptoms of IBS
		2 trials (*n*=160)	0.003	Probiotic: BL2, LP3, LR, LA; prebiotic: FOS		Beneficial for chronic idiopathic constipation treatment
Kinross et al. (2013) [76]	Clinical outcome after elective surgery	8 trials (*n*=361)	0.002	Probiotic: LC, LP2, LP3, LM, LA, LB, BL2, ST, PP, BB, EF, CB, BM, LS, BB2, LL; prebiotic: OAF, OF, BG, I, P, RS, GOS	Patients undergoing elective surgery	The incidence of postoperative sepsis was reduced by synbiotic treatment
		4 trials (*n*=135)	0.03	Probiotic: PP, LM, LP2; prebiotic: BG, I, P, RS		Synbiotics reduced the length of postoperative antibiotic use
		2 or 3 trials each (*n* varying between 198 and 260)	>0.05	Probiotic: LC, LP2, LP3, LM, LA, LB, BL2, ST, PP, BB, EF, CB, BM, LS, BB2, LL; prebiotic: OAF, OF, BG, I, P, RS, GOS		No significant changes were observed for prevention of pneumonia, wound infection, urinary tract infection, mortality, and length of hospital stay
Bessera et al. (2015) [62]	Glycemia, insulin concentrations and lipid parameters	2 trials (*n*=364)	0.04	Probiotic: BL, LC, LR, ST, BB, LA, LB; prebiotic: FOS	Adult patients with overweight or obesity	Reduced plasma fasting insulin concentrations
		3 trials (*n*=260)	<0.05	Probiotic: LS2, BL, LA, BB; prebiotic: I, FOS		Reduced plasma triglyceride concentrations
		2, 3 or 4 trials each (*n* varying between 49 and 104)	NG	Probiotics: LC, LR, ST, BB, LA, BL, LB, LS2; prebiotic: I, FOS		No significant changes were observed for total cholesterol, LDL-c, HDL-c and fasting glucose
Mugambi et al. (2012) [77]	Growth and stool frequency	2 trials (*n*=227)	0.29	Probiotic: BL, LR, LP3; prebiotic: GOS, ScFOS	Infants	Synbiotics failed to improve growth rate but significantly improved stool frequency
		2 trials (*n*=122)	0.006	Probiotic: BL; prebiotic: GOS, FOS		

Probiotic type: BB, *Bifidobacterium breve*; BB2, *Bifidobacterium bifidum*; BL, *Bifidobacterium longum*; BL2, *Bifidobacterium lactis*; BM, *Bacillus mesentericus*; CB, *Clostridium butyricum*; EF, *Enterococcus faecium*; LA, *Lactobacillus acidophilus*; LB, *Lactobacillus bulgaricus*; LC, *Lactobacillus casei*; LL, *Lactococcus lactis*; LM, *Leuconostoc mesenteroides*; LP, *Pediococcus pentoseceus*; LP2, *Lactobacillus plantarum*; LP3, *Lactobacillus paracasei*; LPSP, *Lactobacillus paracasei* subsp. *paracasei*; LR, *Lactobacillus rhamnosus*; LS, *Lactobacillus salivarius*; LS2, *Lactobacillus sporogenes*; PP, *Pediococcus pentosaceus*; ST, *Streptococcus thermophiles*.

Prebiotic type: BG, β-glucan; FOS, fructooligosaccharides; GOS, galactooligosaccharides; HE, hepatic encephalopathy; I, inulin; NG, not given; OAF, oat fiber; OF, oligofructose; P, pectin; RS, resistant starch; Sc, short chain.

Conclusion

More than a century ago, Nobel laureate, Ilya Metchnikoff wrote "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes" [92]. Noting the experimental challenges implied by this goal, Metchnikoff added that "Notwithstanding this difficulty, however, a rational solution of the problem must be sought." These experimental difficulties no longer exist, and the ability to modulate the gastrointestinal microbiota by prebiotic fibers and rational synbiotics is now possible. Current efforts to relate shifts in the microbiota, and specific taxa, in particular, to health and disease or to affect a clinically proven health benefit, may well lead to well tolerated and effective therapies for improving human health. In particular, formulation of synergistic synbiotics containing strains having established health benefits may provide opportunities for personalized treatments.

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Conflicts of interest — None.

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