

Conflicting Results with Use of Probiotics in Severe Acute Pancreatitis

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The results of the Dutch Multicenter PROPATRIA Study ¹ (where use of multiple probiotics led to intestinal ischemia, increased multiple organ failure, and death) were startling enough in their own right, but were even more unexpected because they contradicted two previous studies by Olah ^{2,3} where use of probiotics improved outcome in severe acute pancreatitis. One has to interpret study results that the treatment itself (not an error in randomization or extraneous confounding factor) caused the negative outcome – that the addition of bacteria infused directly into the small bowel set up an adverse cascade of events that led to organ failure and ultimately death. The response to this paper however needs to be framed by the key question: With clear benefit in other critically ill patient populations and two earlier studies specifically in pancreatitis, why did this group do worse? The answer may lie in the possibility that the benefit from probiotics in pancreatitis is a bell-shaped curve – that for a variety of reasons, the group of patients in the PROPATRIA Study fell off the far side of the curve and did worse rather than better.

The explanation for these poor results may be related to the high incidence of gut ischemia seen in the treatment group (where the controls appeared to have none). Investigators fed high doses of enteral nutrition (EN), fiber, and bacteria directly into the small bowel. Pancreatitis is a notorious disease process for problems with third spacing and difficulties in volume resuscitation. Six out of the nine patients who developed

ischemia were fed on pressor agents in a setting of hypotension. Splanchnic hypoperfusion, reduced nutrient absorption, fermentation of luminal formula, and high doses of bacteria might have led to gaseous distention, increased intraluminal pressure, and intramural ischemia, a process that certainly would promote organ failure and death.

A number of similarities exist between the Besselink ¹ and the two Olah reports.^{2,3} All three studies infused probiotics directly into the jejunum twice a day. All three provided specific prebiotic therapy (oat fiber, corn starch, pectin, etc.) in addition to fiber-containing formula. Many differences in the design of the Besselink study, however, set it apart from the Olah studies. The patients in the Dutch study were on the average 15 years older than those patients in the Olah studies, and there was a higher frequency of biliary pancreatitis which tends to be more severe than ethanol-induced pancreatitis. Greater severity of illness and Systemic Inflammatory Response Syndrome was suggested by higher Imrie scores and C-Reactive Protein levels in the Besselink study, but this was offset by lower APACHE II scores and a lower percentage of pancreatic necrosis on CT scan compared to the Olah studies. The Dutch patients, however, received a greater number of probiotic organisms (six types of both *Lactobacillus* and *Bifidobacteria* at 10^{10} CFU/mL (versus one to four types of *Lactobacillus* alone in the Olah studies). Patients were treated with probiotics for a longer period in the Besselink study (4 weeks compared to 1 week in the Olah studies), and the Dutch researchers were very aggressive with the probiotic/enteral nutrition therapy (as evidenced by the fact that feedings were continued on pressor agents in some patients).

It is important to maintain proper perspective of the results of these three studies. The situation is similar to the publication of the Bower study ⁴ in 1995 where a higher mortality seen with an immune formula compared to standard formula in critical illness alerted the nutrition community that such manipulations of EN might be dangerous. However, subsequent studies indicated that the benefit of the immune formulas was real in the right population of patients. ⁵ Studies in pancreatitis have shown that the greater the disease severity, the greater the value and benefit of EN. ⁶ The Besselink study ¹, though, is a reminder that there may be some inherent risk with EN and probiotics. Factors such as older age, under-resuscitation, hypoperfusion on pressor therapy, and greater disease severity may make the risk prohibitive in certain patients. Outcome benefits from probiotics have been shown in other patients with critical illness ⁷⁻¹¹ and in the two previous studies of severe pancreatitis by Olah. ^{2,3} Progress and scientific knowledge is hindered by overreaction. It is important to avoid early, potentially inappropriate generalizations such as: any probiotic is dangerous in the critically ill patient, early EN is too dangerous in severe acute pancreatitis, or that probiotics have no role in therapy of severe acute pancreatitis.

The differences between these three studies raise certain key questions. Does the type of organism or the virulence between strains of Lactobacillus and Bifidobacteria explain the difference between these three studies? Does Bifidobacteria act more readily on fiber with fermentation and gas production than Lactobacillus? Are there important differences between the prebiotics (oat fiber, beta glucan, cornstarch)? How much is too much when prebiotic insoluble fiber is added to a formula already containing fiber? Can

these differences simply be explained by a multicenter versus single center study? Usually a single center misses a signal which is amplified by a larger multicenter trial (Type 2 beta error). Or, a small difference is seen in the single center that turns out not to be significant in the larger study (Type 1 alpha error). The Besselink multicenter trial, however, showed results which were directly opposite to the those from the two earlier Olah studies. Does that mean the weight of the multicenter trial dictates that we should ignore the results from the single center trials?

At this point, a few recommendations can be made as the nutrition community awaits further study. Certainly we need to define measures of adequate fluid volume resuscitation in the management of pancreatitis patients. In severe critical illness, any insoluble fiber should be avoided. Gastric feeds may have an element of greater safety than jejunal feeds (i.e., one should avoid infusion of probiotics and fiber directly into the small bowel). In severe pancreatitis, soluble prebiotic fiber therapy may have a greater element of safety than the direct infusion of probiotic live bacteria. Accurate monitors of tolerance are needed to know when to stop versus when to continue delivery of EN. Certainly more studies in pancreatitis are needed to find the specific strain and dose of probiotic bacteria that might benefit outcome in this difficult patient population.

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Table 1. Comparing Three Probiotic Studies in Pancreatitis

	Olah 2002 ²		Olah 2007 ³		Baseline 2008 ¹	
	Probiotic	Controls	Probiotic	Controls	Probiotic	Controls
	(n=22)	(n=23)	(n=33)	(n=29)	(n=152)	(n=144)
Baseline Comparisons						
APACHE II Scores	8.9	9.4	11.7	10.4	8.6	8.4
Imrie Scores	2.5	2.8	2.9	3.1	3.3	3.4
Mean CRP levels	206	188	216	191	268	270
% EtoH etiology	59%	70%	60%	62%	18%	19%
% Necrosis	41%	48%	60%	62%	30%	24%
Age (yrs)	44.1	46.5	47.5	46.0	60.4	59.0
Study Design						
Centers	Single		Single		Multicenter (n=15)	
Blinding	Double blind		Double blind		Double blind	
Formula	Nutrison Fibre		Nutrison Fibre		Nutrison MultiFiber	
Additional Prebiotic	Oat fiber (10 gm)		Betaglucan inulin Pectin, starch (10 gm)		Cornstarch Maltodextrin	
Organisms	L. plantarum		L. Pediacoccus		L. acidophilus	
			L. leuconostoc		L. casei	
			L. paracasei		L. salivarius	
			L. plantarum (Synbiotic 2000)		L. lactis	
					B. bifidum	
					B. lactis (Ecologic 641, Winclove)	
Dose	10 ⁹		10 ¹⁰ each org		10 ¹⁰ each org	
Location feeds	Nasojejunal		Nasojejunal		Nasojejunal	
Duration Rx	1 week		1 week		4 weeks	
Outcome Results (*p<0.05)						
MOF	9%	8.7%	15.1%	31.0%	22%	10%*
Surg intervention	4.5%	30.4%*	12.1%	24.1%	18%	10%*
Mortality	4.5%	8.7%	6%	21%	16%	6%*
Septic complications			27%	52%	30%	28%
Hosp LOS	13.7d	21.4d	14.9d	19.7d	28.9d	23.5d