LETTER

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Response to "Reassessing the death risk related to probiotics in critically ill patients"

William Manzanares¹ and Paul E. Wischmeyer^{2*}

See related Letter by Maraolo, http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1565-1

We would like to thank Dr. Maraolo for his valuable and careful analysis [1] of the data of our recently published systematic review and meta-analysis on probiotic and synbiotic therapy in the critically ill [2]. As Dr. Maraolo has observed we have made an error in the calculation of the pooled risk ratio (RR) and 95% confidence interval (CI) for the effect of probiotics on hospital mortality. When we abstracted mortality data from the Besselink et al. [3] study we included correct data in both arms (24 of 152 and 9 of 144 patients in the probiotic and placebo groups, respectively). Nonetheless, we made a mistake creating the forest plot. Please, accept our sincere apologies.

Currently, after including the correct data from the Besselink et al. study using the random effect model in the software RevMan 5.3 (Cochrane IMS, Oxford, UK), we found that the revised effect of probiotics and synbiotics therapy on overall mortality is 1.02 (95% CI 0.85,1.22; p = 0.83, $I^2 = 0\%$; Fig. 1). Notwithstanding, at this point we respectfully disagree with Dr. Maraolo. Certainly, after reassessing the RR this new result does not change the direction of the effect against the use of probiotics in the critically ill. Our previous data showed that the RR was 0.98 with a CI similar to the present one (0.85, 1.22). Moreover, the p value was 0.83 and we cannot thus affirm that a trend against probiotics on mortality exists, as we defined trend with a p value <0.10. So far, clinical trials evaluating the effects of probiotics (excluding Saccharomyces boulardii, which should not be considered as a probiotic in the critical care setting) [4] in different ICU patient populations have documented safety and clinical benefits, as we recently demonstrated in our systematic review.

Having said that, the conclusion of our meta-analysis remains unchanged. According to our findings probiotic therapy may be associated with a significant reduction in overall new infections, including new episodes of ventilator-associated pneumonia. However, no benefits in terms of reduction in mortality or another relevant clinical outcome for critically ill patients have been pointed out.

Abbreviations

CI: Confidence interval; RR: Risk ratio.

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Authors' contribution

WM and PW wrote and edited the letter. Both authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethical approval and consent to participate Not applicable.

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Study or Subgroup	Probiotics		Control		Risk Ratio			Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Tempe 1983	3	20	3	20	1.5%	1.00 [0.23, 4.37]	1983	
Kecskes 2003	1	22	2	23	0.6%	0.52 [0.05, 5.36]	2003	
Jain 2004	22	45	20	45	16.3%	1.10 [0.71, 1.71]	2004	+
Lu 2004	2	20	1	20	0.6%	2.00 [0.20, 20.33]	2004	
Klarin 2005	2	8	2	7	1.1%	0.88 [0.16, 4.68]	2005	
McNaught 2005	18	52	18	51	11.5%	0.98 [0.58, 1.66]	2005	
Olah 2007	2	33	6	29	1.4%	0.29 [0.06, 1.34]	2007	
Besselink 2008	24	152	9	144	6.0%	2.53 [1.22, 5.25]	2008	
Klarin 2008	3	22	2	22	1.1%	1.50 [0.28, 8.12]	2008	
Knight 2009	35	130	42	129	22.5%	0.83 [0.57, 1.21]	2009	
Frohmader 2010	5	20	3	25	1.9%	2.08 [0.56, 7.68]	2010	
Morrow 2010	12	68	15	73	6.8%	0.86 [0.43, 1.70]	2010	
Sharma 2011	2	24	2	26	0.9%	1.08 [0.17, 7.10]	2011	
Ferrie 2011	2	18	2	18	0.9%	1.00 [0.16, 6.35]	2011	
Cui 2013	1	23	1	25	0.4%	1.09 [0.07, 16.39]	2013	
Lopez de Toro 2014	19	46	18	43	13.1%	0.99 [0.60, 1.61]	2014	-
Zeng 2016	26	118	25	117	13.5%	1.03 [0.63, 1.68]	2016	+
Total (95% CI)		821		817	100.0%	1.02 [0.85, 1.22]		4
Total events	179		171					
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 12$.15, df =	16 (P	= 0.73);	$^{2} = 0\%$		
Test for overall effect:	Z = 0.21	(P = 0.	.83)					U.UI U.I I IO IO

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References

- Maraolo AE. Reassessing the death risk related to probiotics in critically ill patients. Crit Care. 2016;20:338.
- Manzanares W, Lemieux M, Langlois PL, Wischmeyer PE. Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis. Crit Care. 2016;20:262.
- Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, Van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG, Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind,placebocontrolled trial. Lancet. 2008;371:651–9.
- Urben LM, Wiedmar J, Boettcher E, Cavallazzi R, Martindale RG, McClave SA. Bugs or drugs: are probiotics safe for use in the critically ill? Curr Gastroenterol Rep. 2014;16:388.