

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40145

Title: Five years of fecal microbiota transplantation – an update of the Israeli experience

Reviewer's code: 02941324

Reviewer's country: Italy

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-24

Date reviewed: 2018-08-31

Review time: 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The paper describes the Israeli experience on FMT in patients with recurrent *C. difficile*.
My comments: ABSTRACT - Please define that LGI is represented only by colonoscopy.
Why did you not use enemas? INTRODUCTION - please refer to guidelines on FMT for
CDI when telling that FMT is widely recognized as a treatment for recurrent CDI (e.g.

Surawicz et al, AJG 2013; Debast et al - CMI 2014; Cammarota et al - Gut 2016; Mullish et al - Gut 2018; Sokol et al - DLD 2016) METHODS - What do you mean for variables? In this paragraph you talk about outcomes, please clarify RESULTS - please define, if possible, antibiotic classes used before CDI (e.g. b-lactamics, fluoroquinolones, etc) - You describe several parameters that are correlated with FMT success or failure. I strongly suggest to make this analysis more appropriate with a multivariate analysis. Moreover, I suggest to compare, in the discussion, your results with those achieved by Fischer et al (AJG 2017) and Ianiro et al (Clin Microbiol Infect 2017) that identified predictors of FMT failure. - Please explain which treatment the 5 patients who did not respond FMT and subsequently died were offered before death. - A 10% mortality is quite high for FMT. Please discuss and compare with previous cohorts in the discussion section - How many patients underwent multiple infusions, according to different routes? In two recent metaanalyses (Ianiro et al- UEG Journal 2018; Quraishi et al - APT 2018) the efficacy of single and multiple infusions was stratified for different routes of delivery. Please compare your results with them.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication



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[] Plagiarism

[Y] No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40145

Title: Five years of fecal microbiota transplantation – an update of the Israeli experience

Reviewer's code: 03714458

Reviewer's country: United States

Science editor: Ruo-Yu Ma

Date sent for review: 2018-10-10

Date reviewed: 2018-10-14

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

My edit recs Title: Five years of fecal microbial--> Five years of fecal microbiota
Abstract; in Israel 5 years ago--> in Israel in 2013 - capsules on ambulatory--> capsules to
ambulatory - CDI between 2013 through 2017--> CDI from 2013 through 2017 - upper GI
(UGI)--> upper gastrointestinal (UGI) - of the were 35 (32%) patients--> There were 35

(32%) patients - rate also associated--> rate also correlated Key words: Do not use abbreviation Background; - Edit as ; nasogastric/nasojejunal tube - and it generally occurred--> and generally occurred - Edit as ; donors in a significantly larger number of patients with different disease - Therefore, our aim was to examine whether despite this wide range of patients and FMT dependent variables, the procedure is as effective in all groups of patients and whether a certain FMT route is more effective than others. - consider re-wording to be easier to read; for example " Therefore, our aim was to examine whether FMT continued to demonstrate efficacy despite this wider range of donors and patients, as well as FMT-dependent variables, and to examine the individual FMT routes for efficacy as well. " Results; - Edit as ; excluded due to insufficient follow-up. The median age of the 111 participating - 6 months since FMT initiation --> 6 months after FMT initiation - Edit as ; and another above 60 years of age (mean 77.1±8.9 years, mean difference 39.8, 95% CI 35.3 - 44.3, $p < 0.001$) (Table 4). - Edit as ; in the intensive care unit - Edit as ; The other 5 showed no clinical response Discussions Edit as ; In this multi-center cohort study, we described the real-world experience of FMT procedures for CDI in a heterogeneous national Israeli population during the five years since the procedure has been approved. We examined the distribution of different techniques, routes and success rates in 111 FMT procedures. - Edit as ; and success rates rose to 88% at 2 months. - Edit as ; while Kassam et al reported a trend for higher resolution rates through the LGI route compared with the UGI route - Edit as ; Minnesota, USA, community-acquired CDI accounted for 41% of CDI cases and was characterized by a younger population with less severe disease, which is in line with our findings 21. We found a significantly higher percentage (40%) of IBD patients among this group compared to the older group (8%). Interestingly, the waiting period between first CDI episode to undergoing FMT was longer among the younger patients compared to the older ones, possibly due to a delay in diagnosis or to a lower compliance rate to



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undergo FMT, as well as a lower index of suspicion among physicians caring for younger - - Edit as ; These are important for creating balanced data regarding the efficacy and safety of FMT in real life. Limitations: - Edit as ; There were several limitations in the present study. Firstly, it is retrospective in design, warranting a prospective double-blind randomized placebo-controlled study. Secondly, some of the data were collected a posteriori and information on laboratory findings and Charlson scores of some of the patients (especially in the ambulatory patients) were not available. - any other limitations? Recommend putting power as a limitation, study population (just Israeli patients were included), etc. - need concluding sentence given all the possible limitations of this study - make comments on if the study results here are generalizable to the whole world—would this info be applicable to other countries? - - Generalizability: (Make comments on if the study results here are applicable to other countries or generalizable to the whole world?) - - The results of this study correlate with previous works of others as described in the literature. (Does it correlate with all previous works? If so, specifically how? And if not, how does it not correlate? This paragraph is too short and should be more explanatory). - - For the full data of the cohort, please contact the corresponding author. - make comments on if the study results here are generalizable to the whole world—would this info be applicable to other countries? - - - - In conclusion, FMT is a safe and effective treatment for CDI, which has been occurring in growing numbers in both older and younger populations. While both LGI and capsule administration of FMT seem to be more efficient than the UGI endoscopic route, FMT via capsules has emerged as a successful and well-tolerated alternative. Prospective and well-powered studies are needed to conclusively determine the best route of administration. - would ((also add comments on side effects, costs, ease of administration, safety to patients, potential for insurance to cover the expense, etc



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40145

Title: Five years of fecal microbiota transplantation – an update of the Israeli experience

Reviewer's code: 03327970

Reviewer's country: Sweden

Science editor: Ruo-Yu Ma

Date sent for review: 2018-10-10

Date reviewed: 2018-10-20

Review time: 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
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SPECIFIC COMMENTS TO AUTHORS

This paper presents very nicely different outcomes/parameters regarding the use of FMT for CDI in Israel in the last five years, and provides an important follow-up of CDI patients treated with FMT. There is definitely a need to present more register data as presented in this manuscript on the outcomes of FMT in CDI. Specific comments: 1.

There are more recent, systematic and meta-reviews on FMT in CDI then the ones listed as ref 7-9, please update. 2. The same is true for references 12-14, please update, e.g. with this one: <https://doi.org/10.1111/apt.13868> 3. No mention is made in this paper if frozen or fresh stool was used. Please explain if fresh and/or frozen material was used, and if data is available, consider adding it to Table 3 (Success and Failure). 4. Please include in the first page of the discussion that administration of FMT by capsules also had the highest recurrence rate (although not significant). 5. Please include in the discussion that the highest AE rate in this study was in the LGI group which is different from most other reports (E.g., Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol 2013; 108: 500-8; Furuya-Kanamori L, Doi SA, Paterson DL, et al. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrent or refractory Clostridium difficile infection: a collaborative analysis of individual patient data from 14 studies. J Clin Gastroenterol 2016) 6. According to your data, 18 out of 20 CDI patients that also had IBD were treated with success. Please shortly discuss your data and this article that discuss the lower efficacy of FMT in clearing CDI with IBD compared to without IBD: Khoruts A, Rank KM, Newman KM, et al. Inflammatory bowel disease affects the outcome of fecal microbiota transplantation for recurrent Clostridium difficile infection. Clin Gastroenterol Hepatol 2016; 14: 1433-8. 7. Please clarify in tables 2-5 what the percentage refers to, e.g. using footnotes. Also, what does the sigma stand for? That should be clarified in the methods and the table legends. If no correction for multiple testing was performed, it should be stated both in the methods and the table legends that the reported p-values are descriptive. 8. page 5 line 3 - Israeli instead of Isreali; page 12, line 5 - To maintain continuity with a previous report



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