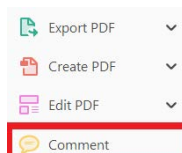


Required software to e-Annotate PDFs: **Adobe Acrobat Professional** or **Adobe Reader** (version 11 or above). (Note that this document uses screenshots from **Adobe Reader DC**.)

The latest version of Acrobat Reader can be downloaded for free at: <http://get.adobe.com/reader/>

Once you have Acrobat Reader open on your computer, click on the **Comment** tab (right-hand panel or under the Tools menu).

This will open up a ribbon panel at the top of the document. Using a tool will place a comment in the right-hand panel. The tools you will use for annotating your proof are shown below:




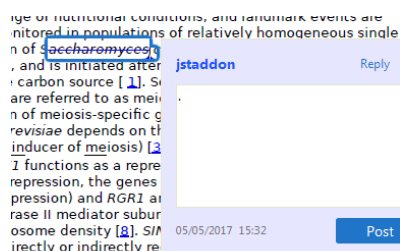
1. Replace (Ins) Tool – for replacing text.



Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it:

- Highlight a word or sentence.
- Click on .
- Type the replacement text into the blue box that appears.




2. Strikethrough (Del) Tool – for deleting text.



Strikes a red line through text that is to be deleted.

How to use it:

- Highlight a word or sentence.
- Click on .
- The text will be struck out in red.

experimental data if available. For ORFs to be had to meet all of the following criteria:



1. Small size (35-250 amino acids).
2. Absence of similarity to known proteins.
3. Absence of functional data which could not be the real overlapping gene.
4. Greater than 25% overlap at the N-terminus terminus with another coding feature; over both ends; or ORF containing a tRNA.


3. Commenting Tool – for highlighting a section to be changed to bold or italic or for general comments.



Use these 2 tools to highlight the text where a comment is then made.

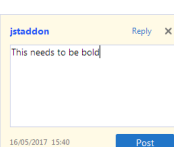
How to use it:

- Click on .
- Click and drag over the text you need to highlight for the comment you will add.
- Click on .
- Click close to the text you just highlighted.
- Type any instructions regarding the text to be altered into the box that appears.

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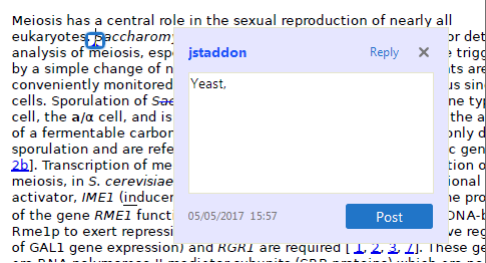
4. Insert Tool – for inserting missing text at specific points in the text.



Marks an insertion point in the text and opens up a text box where comments can be entered.

How to use it:

- Click on .
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the box that appears.



5. Attach File Tool – for inserting large amounts of text or replacement figures.



Inserts an icon linking to the attached file in the appropriate place in the text.

How to use it:

- Click on .
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

The attachment appears in the right-hand panel.

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6. Add stamp Tool – for approving a proof if no corrections are required.



Inserts a selected stamp onto an appropriate place in the proof.

How to use it:

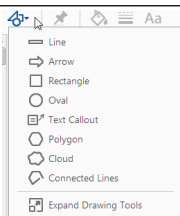
- Click on .
- Select the stamp you want to use. (The [Approved](#) stamp is usually available directly in the menu that appears. Others are shown under *Dynamic*, *Sign Here*, *Standard Business*).
- Fill in any details and then click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

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Drawing tools available on comment ribbon

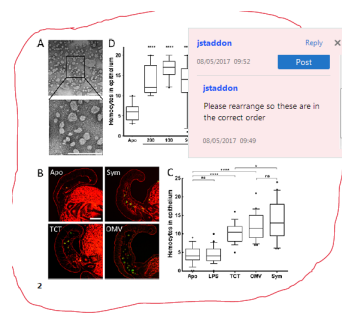


7. Drawing Markups Tools – for drawing shapes, lines, and freeform annotations on proofs and commenting on these marks.

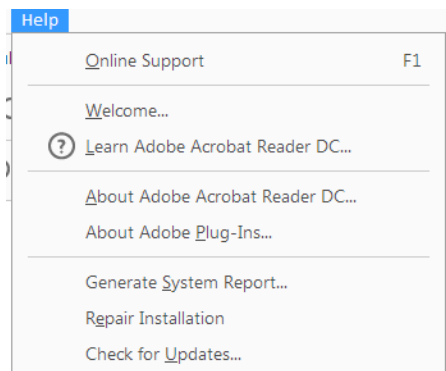
Allows shapes, lines, and freeform annotations to be drawn on proofs and for comments to be made on these marks.

How to use it:

- Click on one of the shapes in the [Drawing Markups](#) section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, right-click on shape and select *Open Pop-up Note*.
- Type any text in the red box that appears.



For further information on how to annotate proofs, click on the [Help](#) menu to reveal a list of further options:



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6	AUTHOR: Table 1 was not cited in the text. An attempt has been made to insert the table into a relevant point in the text - please check that this is OK. If not, please provide clear guidance on where it should be cited in the text.	
7	AUTHOR: Please provide volume and page range for reference [5].	

LETTER TO THE EDITOR

Probiotics for recurrent idiopathic aphthous stomatitis in adults: a placebo-controlled randomized trial

Editor

Sir, recurrent idiopathic aphthous stomatitis (RIAS) is a frequent disorder that induces a marked alteration of the quality of life of affected individuals. Thalidomide is the only treatment that demonstrated its efficacy in a multicenter placebo-controlled trial.¹ However, the use of thalidomide is limited by its side-effects and it is usually reserved for the most severe cases. For milder cases of RIAS, the therapeutic options remain limited and patients often seek for alternative treatments. Interestingly, a dysbiosis in mucosal and salivary microbiota has been reported in RIAS.² The objective of this

study was to assess the efficacy of probiotics on RIAS (Fig. 1).

We performed a monocentric randomized parallel group, double blind, placebo-controlled, study in the Department of Dermatology of Nice University hospital over a two years period. Eligible participants were aged 18 or over, with history of RIAS (at least one new aphthous lesion each month during the past 6 months). After central randomization, patients were allocated to received oral suspension of 1.5 billion *Lactobacillus rhamnosus* Lcr35® (Bacilor®, Lyocentre laboratories) or placebo, four times a day for 3 months. If needed, patients could use clobetasol cream for maximum twice a day. The tubes were weighted at the end of the study to quantify their consumption. Patients were then followed for three additional months. The primary end point was the number of canker sores in the third month of treatment as compared to the month before the onset of the study. The secondary end points were the number of canker sores during the 3-month follow-up, the pain induced by the lesions [assessed using a visual analogic scale (VAS)], the

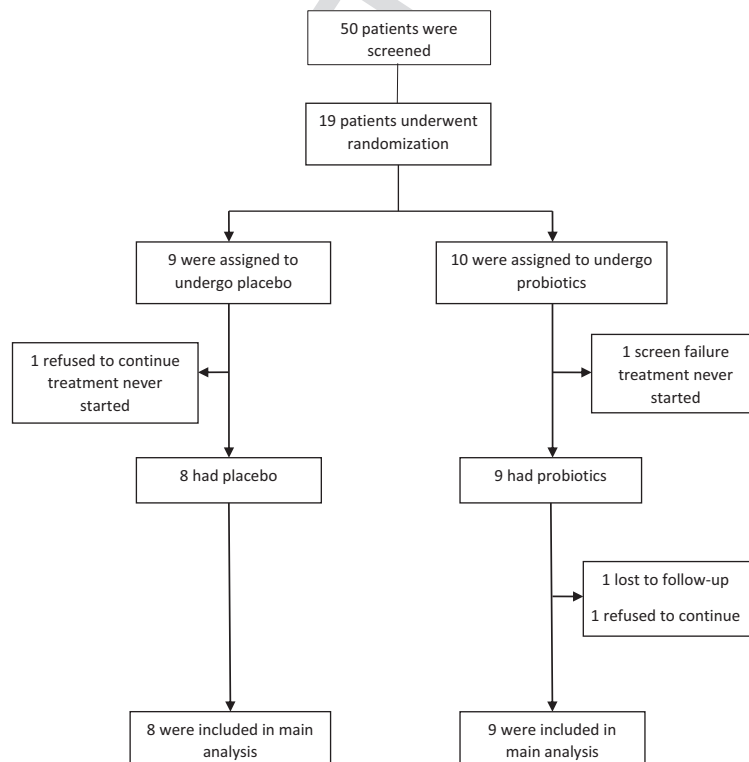


Figure 1 Flow diagram of the study.

Table 1 Patients' demographics at baseline

	<i>n</i>	Placebo group (<i>n</i> = 9) %	<i>n</i>	Probiotic group (<i>n</i> = 10) %
Age (years), Mean (\pm SD)	9	36.4 (12.2)	10	55.9 (17.5)
Sex				
Male	4	44.4	4	40.0
Female	5	55.6	6	60.0
New aphthae last month Mean (\pm SD)	9	11.9 (10.8)	10	4.2 (1.93)
Time since aphthosis diagnosis (years), Mean (\pm SD)	9	12.9 (11.7)	10	15.5 (16.9)
Previous treatments				
Topical steroids	4	44.4	0	0
Colchicine	2	22.2	4	40
Systemic steroids	2	22.2	2	20
Thalidomide	0	0	0	0

satisfaction of the patients (assessed by a VAS), and the quality of life evaluated by the Oral Health Impact Profile 14 questionnaire.³ In order to detect a difference of two lesions per month between the two groups with an alpha risk of 5% and a beta risk of 90%, we calculated that seven patients were needed in each group. Analysis of Covariance (ANCOVA) was used for the main and secondary endpoints, except for the impact on the quality of life that was assessed using Wilcoxon test (Table 1).

A total of 50 patients were screened, and 19 patients were randomized (9 in placebo group; 10 in probiotic group). Two patients were excluded from analysis because they didn't start the treatment, and 17 patients (8 placebo group; 9 probiotic group) were thus included in the intention to treat analysis. The mean duration of the disease was 12.9 years in the placebo group and 15.5 years in the probiotic group. After 3 months of treatment, the average decrease of canker sores in placebo group was -3.55 ± 1.80 IC95% $[-7.42; 0.32]$, $P = 0.07$, vs. -0.73 ± 1.69 IC95% $[-4.35; 2.88]$, $P = 0.67$ in probiotic group. There is no significant difference between the 2 groups (-2.81 IC95% $[-8.52; 2.89]$, $P = 0.3$). After 6 months, the average decrease of canker sores compared to baseline in placebo group was -3.93 ± 0.79 IC95% $[-5.62 \text{ to } -2.23]$, $P < 0.001$, vs. -2.95 ± 0.74 IC95% $[-4.53 \text{ to } -1.37]$, $P = 0.0013$ in probiotic group. There is no significant difference between the two groups (-0.98 IC95% $[-3.48 \text{ to } 1.52]$ $P = 0.4$). No statistical differences were also noted between the two groups when assessing the consumption of topical steroids, the pain, the satisfaction, and the quality of life. Results of the secondary endpoints are presented in the Table S1. The compliance was good in the two groups. No serious side effect was reported.

Probiotics have been reported to be potentially useful in patients with cavities, periodontitis, and gingivitis.⁴ A recent trial assessing another strain of probiotics in RIAS did not find either any difference between groups.⁵ Taken together these data do not support the use of probiotics in the treatment of RIAS in adults. The placebo and probiotics were provided by Lyocentre laboratories.

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IRB approval status: Comité de Protection des Personnes Sud Méditerranéen V. No 2015-003944-38). National French Agency for Medicine approval: 151212A-32).
ClinicalTrials.gov registry: NCT02789605

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Secondary outcomes.

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