

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Eosinophils in the oesophageal mucosa - Clinical, pathological and epidemiological relevance in children: A Cohort Study
AUTHORS	Marta C Cohen, Prithviraj Rao, Mike Thomson, Mudher Al-Adnani

VERSION 1 - REVIEW

REVIEWER	Paola Domizio Professor of Pathology Education/Honorary Consultant Histopathologist Barts and the London School of Medicine and Dentistry/Barts and the London NHS Trust United Kingdom No competing interests
REVIEW RETURNED	09/11/2011

THE STUDY	No statistics employed in this paper; none would be appropriate
GENERAL COMMENTS	<p>This paper from a tertiary paediatric referral centre reports a retrospective study of oesophageal eosinophilia in children presenting over a two year period. It makes a valuable contribution to the growing literature on this subject. On the whole the article is well written and presented. The photomicrographs are clear and the tables are comprehensive. The number of patients studied (24) is relatively small, though it is a larger number than most centres would expect to see over the same time period. At over 3500 words, the paper is on the long side for an article in the BMJ.</p> <p>My specific comments are as follows: The Methods section states that "<i>All oesophageal biopsies with ≥ 15 eosinophils/high power fieldwere retrieved</i>". I presume this should state "with an average of 15 eosinophils per high power field" otherwise the statement in the Results section that the number of eosinophils ranged from 4 (which is obviously less than 15) - 57per high power field would seem to contradict this. The lack of consensus on the eosinophil count required to diagnose eosinophilic oesophagitis is mentioned in the Discussions section. This should, however, be pointed out earlier and a clear statement made as to which diagnostic criteria have been used (eg</p>

	<p>the AGA recommendations cited in reference 10). Para 4 line 1 of the Results section states that <i>“No eosinophils were seen infiltrating the mucosa in 1/36 biopsies but eosinophils were present in other biopsies from the same patient”</i>. This is confusing. Does it mean that no eosinophils were seen in one biopsy from one patient, but in another biopsy from the same patient, the threshold value was reached? The next sentence states <i>“The average number of eosinophils in the remaining 34 biopsies was 32...”</i> Should this not be 35 biopsies (36-1=35)? Para 5 lines 6-8 of the Results section state that <i>“8 biopsies contained a small amount of superficial lamina propria. Therefore the presence or absence of fibrosis could not be assessed.”</i> This is confusing. Does this mean that eight biopsies contained some lamina propria but not enough to assess whether or not fibrosis was present or that none of the 36 biopsies contained sufficient lamina propria for assessment of fibrosis (as inferred from the second sentence)? There are a considerable number of grammatical and typographical errors, however. These are too many to list individually, but some examples are listed here: Title: “oesohageal” should read “oesophageal” P7 line 11 “with not response” should read “with no response” P7 line 13 “no pH study had not been performed” This double negative makes no sense In addition, the way that numerals from 1-9 are expressed lacks consistency. In some places they are written as numerals, in others they are written as words.</p>
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REVIEWER	Jorge Amil Dias Hospital S. João, Porto, PORTUGAL No conflict of interests.
REVIEW RETURNED	11/11/2011

THE STUDY	The retrospective nature of the study hampers some conclusions as not all patients underwent the full diagnostic protocol.
RESULTS & CONCLUSIONS	As meniotned above, the true relation between EO and GORD cannot be extrapolated but merely identified as possible.
GENERAL COMMENTS	Interesting manuscript but with some limitations derived from the retorspective nature of the study. These should be addressed. Discussion is too long: there are various considerations beyond the true scope of the study; some items would be more adequate in a review paper; there are some unnecessary repetitions of results in the discussion. The limited number of patients that underwent evaluation for GORD limits the conclusions about Overlap Syndrome and should be expressed with some caution about its true incidence.

VERSION 1 – AUTHOR RESPONSE

Prof Paola Domizio:

1. M&M: it now describes that oesophageal biopsies retrieved were those “ with an average of 15 eosinophils per high power field”
2. Discussion: The lack of consensus on the eosinophil count required to diagnose eosinophilic oesophagitis is now pointed out earlier and a clear statement made as to which diagnostic criteria is used at our institution.
3. Para 4 line 1 of the Results section. The sentence that resulted confusing was deleted. A short statement now reads: “A total of 36 oesophageal biopsies were performed in the 24 patients of the study; although only 35/36 biopsies fulfilled the criteria of EO (this patient had another simultaneous biopsy with EO)”. The next sentence now reads “ The average number of eosinophils in the 35 biopsies from the 24 cases of the study”...
4. Para 5 lines 6-8 of the Results section : the sentence was clarified. This now reads: “Most biopsies did not include lamina propria and only 8 biopsies contained a small amount of superficial lamina propria. Therefore, the presence or absence of fibrosis could not be assessed.”
5. Grammatical and typographical errors were reviewed and amended.

Dr Jorge Amil Dias:

6. The following statement was added as one of the limitations of the study: “The small number of patients that underwent full evaluation for GORD limits the conclusions about Overlap Syndrome”
7. The discussion was shortened.
8. Less emphasis was given to the relation between EO and IL-5 (the sentence starts : “ Some authors postulate that EO is a IL-5 driven inflammatory disorder...”).

VERSION 2 – REVIEW

REVIEWER	Paola Domizio Professor of Pathology Education/Honorary Consultant Histopathologist Barts and the London School of Medicine and Dentistry/Barts and the London NHS Trust United Kingdom No competing interests
REVIEW RETURNED	25/11/2011

GENERAL COMMENTS	The revised paper is improved but could still be improved further: Para 35 line 4 of the Discussion states that “ <i>The incidence of oesophageal eosinophila.....</i> ”. I cannot see a definition of “oesophageal eosinophilia” in the paper at any point. How does this differ from EO? Para 10 line 2 of the discussion, sentence beginning “ <i>However, and although...these suggest that there is overlap in the clinical and histological features of GORD</i> ”. I find this sentence confusing. Specifically it is not immediately obvious what is being referred to by “these” (underlined above). There are still a considerable number of grammatical and typographical errors, for example: P4 line 19 “patients were GORD” should read “patients in whom GORD”
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	<p>P4 line 32 “confronted to an oesophageal biopsy with” should read “confronted with an oesophageal biopsy showing”</p> <p>P4 line 35 “These lead us to seek correlation” should read “These led us to seek a correlation”</p> <p>P5 line 6 “with an average of 15 eosinophils” Should read “with an average of at least 15 eosinophils”</p> <p>P6 line 5 “The cases corresponded to” should read “There were”</p> <p>P9 line 14 “associated to” should read “associated with”</p> <p>P9 line 23 “EO is a IL-5-driven” should read “EO is an IL-5 driven”</p> <p>P9 line 31 “although did not have clinical” should read “although not showing clinical”</p> <p>The way that numerals from 1-9 are expressed still lacks consistency. In some places they are written as numerals, in others they are written as words. Numerals over 10 are in places written as words eg. in the Results line 1, “24” is written as “twenty four”.</p>
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VERSION 2 – AUTHOR RESPONSE

We introduced the following changes recommended by Prof Paola Domizio:

Para 35 line 4 of the Discussion.... How does eosinophilia differs from EO? The paragraph now reads:

“The concept of EO is more complex than the simple presence of eosinophils in the mucosa. In EO the occurrence of > 15-20 eosinophils//HPF is restricted to the oesophagus and these have a preferential localization near the surface of the epithelium in a background of basal cell hyperplasia and papillary elongation. Many studies also indicate that in EO, GORD needs to be excluded by normal pH monitoring and failure to respond to high dose proton pump inhibitor therapy [8,9,10]”.

Para 10 line 2 of the discussion was clarified. The sentence now reads:

“However, and although our results are limited due to the retrospective nature of the study and the small number of cases, our findings -in agreement with those obtained by other authors [25,42,43]- ...”

We are grateful to Prof Domizio for her correction of the grammatical and typographical errors. The following were amended:

P4 line 19 “patients were GORD” reads “patients in whom GORD”

P4 line 32 “confronted to an oesophageal biopsy with” reads “confronted with an oesophageal biopsy showing”

P4 line 35 “These lead us to seek correlation” reads “These led us to seek a correlation”

P5 line 6 “with an average of 15 eosinophils” reads “with an average of at least 15 eosinophils”

P6 line 5 “The cases corresponded to” reads “There were”

P9 line 14 “associated to” reads “associated with”

P9 line 23 “EO is a IL-5-driven” reads “EO is an IL-5 driven”

P9 line 31 “although did not have clinical” reads “although not showing clinical”

Numerals are now consistently written as such.

Looking forward to hearing from you in due course

Kind regards

Dr Marta Cohen

On behalf of all authors