Author's response to reviews

Title: Cough and reflux esophagitis in children: their co-existence and airway cellularity

Authors:

Anne B Chang (annechang@ausdoctors.net)
Nancy C Cox (Nancy_Cox@health.qld.gov.au)
Joan Faoagali (Joan_Faoagali@health.qld.gov.au)
Geoffrey J Cleghorn (g.cleghorn@mailbox.uq.edu.au)
Christopher Beem (g.cleghorn@mailbox.uq.edu.au)
Looi C Ee (Looi_Ee@health.qld.gov.au)
Geoffrey D Withers (Geoffrey_Withers@health.qld.gov.au)
Mark K Patrick (docmpatrick@bigpond.com)
Peter J Lewindon (p.lewindon@mailbox.uq.edu.au)

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Dear editor

BMC Paediatrics

Re: Revised manuscript MS: 1775148030775455 - 'Cough and reflux esophagitis in children: their co-existence and airway cellularity'

Thank you very much for reviewing our article and its provisional acceptance, as well as for the opportunity to respond to the reviewers’ comments, which we believe we have adequately addressed below. We hope it is now suitable for publication in BMC Paediatrics.

Thank you again.

With kind regards

Yours sincerely

Anne B Chang, on behalf of co-authors
Response to reviewer 1

Major comments

1. Reviewer’s point “The premise in this study that oesophageal reflux causing respiratory symptoms is related to biopsy proven reflux oesophagitis is at the heart of understanding this paper’s conclusion. The authors effectively prove that this is not so. Given what we know already about reflux associated with respiratory disease this is hardly surprising, but the manuscript is written as if reflux oesophagitis is ‘the gold standard’ for reflux disease. Laryngopharyngeal reflux causing respiratory symptoms is poorly correlated to oesophageal inflammation. If the manuscript were altered to reflect this rather than to doubt whether reflux was associated with cough then it would be much nearer the truth. In fact the authors have no evidence that reflux is not associated with the patient’s cough merely that the oesophagitis is not”.

Response: One of the difficulties in the issue of GER and respiratory diseases (cough, asthma, etc) is that it is controversial. There are some believers and some sceptics. When examined at the level of evidence based medicine, the two Cochrane reviews (P. G. Gibson, R Henry, J. Coughlan. Gastro-oesophageal reflux treatment for asthma in adults and children. The Cochrane Library Issue 1, 2003 and A. B. Chang, T. Lasserson, J Gaffney, F. C. Connor, L. A. Garske. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. The Cochrane Database of Systematic Reviews:Issue 2, 2005) on this subject has highlighted the controversy and showed that the association is not as strong as that widely believed. The Cochrane review on cough and GER also showed included data on upper airway symptoms ie what the Prof Morice has termed ‘Laryngopharyngeal reflux’. In the paediatric literature (as this is purely in children we are restricting discussion to children when relevant), the North American Society for Pediatric Gastroenterology and Nutrition (NASPGAN) guidelines for pediatric GER the section on upper airway symptoms included a discussion on cough and GER. The conclusion reached in the section was “…there is insufficient evidence and experience in children for a uniform approach to diagnosis and treatment”. [Rudolph CD, Mazur LJ, Liptak GS et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32 Suppl 2:S1-31].

Biopsy proven reflux esophagitis is indeed the gold standard of the diagnosis of GERD as quoted in the original manuscript (Discussion section, 2nd last para). The quote from the
American Gastroenterology Association was “In the absence of esophagitis, there is no gold standard for the definition of GERD...” [American Gastroenterological Association medical position statement: guidelines on the use of esophageal pH recording. Gastroenterology 1996, 110: 1981-1996].

2. Reviewer’s point “The discussion concerning reflux treatment is naïve. Most treatment has, up until recently, been designed to relieve the strongly acid related symptoms of heartburn. Treating laryngopharyngeal reflux is much less successful with proton pump inhibitors and the absence of treatment success does not mean that the symptoms are due to reflux”.

Response: We totally agree that “Treating laryngopharyngeal reflux is much less successful with proton pump inhibitors and the absence of treatment success does not mean that the symptoms are due to reflux”. Indeed that is the premise of the study ie association does not imply cause and effect. Prof Morice is (we assume, referring to fundoplication as the treatment of choice for laryngopharyngeal reflux) and a recent review [E. Hassall. Outcomes of fundoplication: causes for concern, newer options. Arch Dis Child 90 (10):1047-1052, 2005] in children (as opposed to adults) does not support his stance that is based on adults.

We had discussed the limitations of our study ie our data refers to RE and not to all types of GER (however defined), as mentioned by Prof Kastelik. Nevertheless we have added a few sentences and the concept of “laryngopharyngeal reflux” to the discussion section in the revised manuscript (last few sentences of 2nd last para in the ‘Discussion’ section).

3. Reviewer’s point “The questionnaire deals only with classic symptoms of reflux and not with those symptoms known to be due to laryngopharyngeal reflux. Thus change in the quality of the voice is a well described symptom of LPR. Cough on lying down is ignored. Are symptoms at night predictive of reflux or not? The LOS closes at night and reflux cough diminishes.”

Response: Data above relates to studies on adults. The only question on nocturnal symptoms was question E in Table 1 where was no association with RE was found. The problem about night-time cough is that it is poorly reported when compared to objective studies, as shown in both adults and children [J. Y. Hsu, R. A. Stone, R. B. Logan-Sinclair, M. Worsdell, C. M. Busst, K. F. Chung. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J 7:1246-1253, 1994; and A. B. Chang, R. G.

Minor comments

4. Reviewer’s point “Results are frequently expressed to two decimal places, surely this is overkill”.
Response: We disagree that expression to 2 decimal points for laboratory is excessive. We had done this in our previous papers on this subject. As this was not requested by Reviewer 2, we have left the results as such.

Discretionary comment

5. Reviewer’s point “An interesting finding was the differential microbial culture from coughers and non coughers (why do the authors invent C+ C- when plain English would be more than adequate). They claim that it is very unlikely that this reflects aspiration and quote what looks like an abstract to support this. Whatever the evidence they show in that piece of work mechanically aspirating gastric contents may well not reflect BAL bacteriology since only certain bacteria prosper within the airways. Similarly the difference between paediatric and adult cough is referred to a paper in press and is thus unsubstantiated as far as this referee is concerned”.
Response: We chose to use C+ and C- for simplification purposes ie as opposed to repeating the phrases ‘children with cough’ and ‘children without cough’. The paper mentioned above was not an abstract but published in the 2nd highest ranking respiratory journal (Respiratory Research) at time of submission and is an open access journal (a BioMedical Central journal). Similarly the second paper referred to (published by invitation also in an open access BioMedical Central journal on 20th Sept 2005), was available on-line on the date of review given on the review file (6th Oct 2005).
**Reviewer 2**

Thank you for the kind comments.

**Minor comments**

1. Reviewer’s point “The Introduction section may benefit from a short description of previous studies that examined BAL cellular content in patients with cough (eg McGarvey et al ERJ 1999;13:59-65) and GERD”.

Response: The paper above has been added (line 2-4 in introduction) and thank you for the suggestion. Several other papers on cough and GER in children were already in the manuscript (discussion section).

2. Reviewer’s point “The authors hypothesised that airways neutrophilia will be more likely in children with cough. Are there any previous studies to support their hypothesis?”

Response: Yes, we quoted the paper published by Fitch et al (ref #9 in original manuscript).

3. Reviewer’s point “Minor mistake in the Results section of the Abstract 3rd line (7,IQR 28) should read (7,IQR 4). The data describes an important relationship between cough and GERD in children. In fact, the authors found that in children without lung disease the co-existence of GERD and cough are common and independent of RE.”

Response: Thank you for the suggestion but there was no error in the abstract, data is the same as presented in Table 2 ie median neutrophil % was 7, IQR 28 in the C+G- group.

4. Reviewer’s point “The authors reported the highest neutrophilia in children with cough without RE and suggested that the most likely explanation for airway neutrophilia is related to airway bacterial infection and not to RE. Can the authors suggest any other possible explanations for their findings? Is it possible that inflammation can contribute to this finding? Surprisingly, no airway eosinophilia was found on BAL. Can the authors comment on this finding?”

Response: The issues of lack of eosinophils and other causes of airway neutrophilia have been added to the discussion (pg 10, last few lines of para 2). We cannot provide any other explanation for airway neutrophilia; given that bacterial bronchitis is known to cause airway neutrophilia and that we found a high number with bacterial bronchitis in our cohort, it would be biological logical that the airway neutrophilia found is related to bacterial bronchitis.