REVIEWERS COMMENTS	AUTHOR RESPONSE
General Comments to the Author: **Reviewer #1** Well done!! **Reviewer #2** The strengths of this guideline on severe asthma are first, that the set-up is modular with questions that are relevant to clinical practice. Second, the PICO approach is straightforward and practical. Third, the figures and algorithms are beautiful and to-the point. There are also weaknesses: The PICO 1 is much less well-founded than the other PICOs. In several paragraphs the evidence is outdated, and needs to be adjusted. Many references do not match with the text, and there are differences in style between the different parts of the guideline. **Reviewer #3** Comprehensive approach to current therapeutic options. May want to give some guidance on current gaps. **Reviewer #4 - CRGC** Bravo. Outstanding. World-class. An incredible piece of work!!	**Re: Reviewer #2:** - PICO 1 has been revised for clarity: *"What is the difference between uncontrolled asthma and severe asthma?"* - The references have been updated in this section - Style has been revised somewhat. **Re: Reviewer #3:** - Current gaps section added tot he end of the document, including – lack of evidence to guide decisions re: which biologic when patients are eligible for more than 1; comparative studies of macrolides vs biologics;
Major Comments: **Reviewer #2 - Major Comments:** 1. Page 4: *Formulation of Key Clinical Questions:* Although asthma exacerbations are a very important outcome, decreasing (or stopping) chronic oral corticosteroid use is at least as important, in view of the serious adverse effects of this medication. 2. On page 8, paragraph 2 says: "Individuals that are truly steroid-dependent based on current best available evidence, may be candidates for mepolizumab and benralizumab (when approved) because of their documented steroid sparing effect". Thus it would have been logic to also include oral corticosteroid reduction as an important outcome of PICO questions. 3. Page 8, PICO 1, key message 1. The diagnosis of asthma is based on the Canadian Thoracic Society 2012 guideline update, in which it says in relation to "confirmed asthma diagnosis": <<*Pulmonary function criteria supportive of an asthma diagnosis include: spirometry showing reversible airway obstruction, peak expiratory flow (PEF) variability, and a positive challenge test such as methacholine or exercise challenge*>>
However, patients with truly severe asthma often do not show reversible airways obstruction, and methacholine or exercise challenge tests cannot be done in a standardized way in these patients, because they cannot refrain from bronchodilator drugs, which is essential for a reliable test result. How do the authors deal with this issue?	**Re: Reviewer #2:** 1. This is very true, and those outcomes were examined. We have added the following sentence: *"Other key secondary outcomes examined included: decreasing (or stopping) chronic oral corticosteroid use, symptoms, asthma control, quality of life and lung function parameters."* 2. Agree. This has been revised as above. 3. The reviewer raises a valid question, which is not addressed in the ERS/ATS definition of Severe Asthma which was adapted by our Clinical Assembly. In practice, many severe asthma patients have historic evidence of reversibility, or changes in lung function over time or for brief medication 'holds'. Discussion of this challenge has been added to the document. "*While the importance of basing an asthma diagnosis on objective measures must be advised, this can often be challenging in individuals with truly severe asthma for several reasons. Adults with long-standing asthma may have limited or no reversibility due to airway remodelling, and/or may be unable to withhold bronchodilator medications to perform methacholine or exercise challenge tests. Over time, variation in ariflow rates during exacerbations may be noted that meet diagnostic critiria. In the absence of such evidence, a thorough search for*

	previous pulmonary function tests should be undertaken, as well as a comprehensive evaluation for alternative diagnoses before making a clinical diagnosis of severe asthma."
4. Page 8, PICO 1, key message 4: In the PICO-1 text, there are no supporting arguments for key message 4. Maybe better to add this key message to PICO-2?	4. References for the key message on adherence have been added to the document.
5. Page 9, paragraph 2: The Th2 pathway is only one of the (multiple) Type-2 pathways. For example, another important type-2- pathway is the innate lymphoid Cell-2 (ILC-2) pathway, which is not mediated by Th2 cells. So, I would reformulate this paragraph in such manner that also non-Th2 pathways leading to eosinophilic inflammation are covered. Same counts for Section 6, Introduction.	5. An explanatory sentence has been added to Page 9 paragraph 2 to clarify that other cells are involved in production of Type 2 cytokines. However, as the literature typically uses the term Th2 high/low these terms have been kept in the paper". The literature typically refers to the Th2 pathway or Th2 high and low groups in recognition of the Type 2 T helper cell which was thought to be main producer of these cytokines. However, it is now recognized that other cell types, such as Type 2 innate lymphoid cells also produce these Type 2 cytokines"
Reviewer #3	**Re: Reviewer #3:**
1. Page 3 **- Target users:** ER doctors and primary care practitioners are listed as target users – but you may want to give some context as to the expectations for some users since the recommended testing and history may not be similar.	1. ER doctors would not be expected to prescribe, but should be familiar with the novel therapies as these patients will frequent their departments.
2. Page 3 - **Methodology:** This section appears vague as to how the literature was ascertained and may be subject to bias. How was the literature review conducted (ie., a librarian, which databases, search terms etc) and what are the CTS requirements for a position statement?	2. This section has been edited for clarity. The searches were done by experienced assembly members, not librarians, which meets the CTS requirements for a position paper.
3. Page 5 - **PICO 1:** The statement says that only one of the statements needs to be met for a label of "severe asthma" to be made. One of the statements is airflow limitation of FEV1< 80% in children – this should be changed to LLN and/or? Reduced FEV/FVC < LLN – is this correct since it appears that lung function alone without symptoms or exacerbations can qualify a subject for severe asthma.	3. Page 5 - A) The criteria have been corrected to LLN B) Only 1 of the 4 criteria for uncontrolled needs to be met, plus the 'preamble'. This is the ATS/ERS formatting of the definition.
Page 6 - **Table 2 –** Does daytime symptoms include exercise induced symptoms?	Page 6 - Yes, it includes exercise-induced symptoms.
4. Page 8 - **PICO 1 –** Key Messages: Key messages 3 and 4 recommend in-depth assessments with phenotyping being a recommendation – in essence you are recommending a "specialist in asthma" referral – why not just make that suggestion? If the costs of biologics are covered in Ontario for pediatrics – I think an "asthma specialist" referral would be warranted to decrease overuse without tackling difficult asthma. Also, guidelines for "asthma specialist" can be defined – ie., those with access to lung function, asthma educator and FeNO +/- sputum. I would add an additional outcome of assessment of phenotype during exacerbation may be particularly helpful in characterizing endotypes.	4. A new key message has been included re: specialist referral, as well as an operational 'definition' so to speak of 'asthma specialist'. In addition, a sentence has been added to the last PICO1 key message re: phenotype assessmsent during exacerbations.

5. Page 12 - **PICO 2** – Very well written and synthesized Key Messages: For Key message 1 – I would split into 2 messages – 1st – sputum eos may be useful to identify anti-IL5 responders 2nd – sputum has not been helpful to identify macrolide responders (but I couldn't see if any literature was reviewed on sputum during exacerbations as a predictor of macrolide response).	5. For consistency, we have kept this as one key message as there is meant to be one key message for each biomarker. Literature assessing biomarkers for macrolide response was taken from studies evaluating chronic macrolide use which only completed biomarker assessment at study entry and not during exacerbations.
6. Page 17 **- PICO 4** – See above – again does the inflammatory response during exacerbations predict macrolide response?	6. See above comment regarding biomarkers for macrolides.
7. Page 20 - **PICO 5 -** Key Messages For Key message 1 – the word "IgE" is missing in the sentence " sensitized to at least perennial allergen and have serum – between 30 and 1300". For the pediatric indication – any comment on severe asthma vs difficult asthma	7. Have added in IgE. Although anti IgE drugs have been shown to be beneficial in pediatric inner city populations ("difficult asthma"), this position statement is only dealing with "severe asthma"
Page 20 - Key message 3 – predictor of response is listed as those with recurrent exacerbations – but since that is a necessary factor to qualify for medication use – can we truly use it as a predictor?	Page 20. Key message 3. Other indications for omalizumab include poorly controlled asthma even without exacerbations, thus we included exacerbations as a separate predictor.
8. **PICO 6** Page 24 - Conclusions- the second last sentence defines "peripheral blood eos in the normative range" – but is that necessary – what if the eos are in a very high range – is that a contraindication?	8. This has been rephrased to clarify that peripheral eos should be above the levels indicated by approved/regulatory bodies; which in fact may include both 'normal' and 'elevated' eosinophils.
Page 24 - **PICO 6 –** Key Messages: For the first key message – I would change to "Anti-IL5 therapies are approved for use in adults aged 18 years and over" rather than "may be considered" – they may also be considered useful for younger than 18 – but will not be approved in the short-term	We thank the reviewer for this comment, but we have not modified this phrasing. Our recommendations provide guidance to clinicians, which may or may not be completely aligned with regulatory approvals. In this case, we are saying it can be considered (we agree with the approval). We are not currently saying they should be considered in younger than 18 (nor are they approved).
Reviewer #4 - CRGC Figure 2: The figure is excellent. I do have one substantial concern for the clinical assembly to address.	
Our general continuum diagram is founded on the principle of escalating therapy from left to right. For example, one starts with low-dose inhaled corticosteroid, and when appropriate increased to ICS/laba, and so on. Similarly, we read from left to right. These two factors contribute to a substantial risk that the reader may interpret the severe asthma management continuum as recommending Xolair as an intervention that should occur logically before macrolides and anti-IL-5 therapy. Of course, this approach is not supported in the text nor is it intended by the clinical assembly.	Addressed in the continuum.
I understand that the accurate positioning of both of these molecules is dealt with in the text and somewhat in the figure	

legend. I do not think this is sufficient to avoid an unintended interpretation giving Xolair primacy over anti-IL-5. I therefore, strongly recommend that it be made clear on the figure itself that the CTS is not endorsing a practice that places Xolair before anti-IL-5 therapy. Consider adding a box or a qualifier of some sort visible on the figure. Please format all Boxes by placing a text box around the key message similar to what was done for the severe asthma definition prior to submission to the journal.	Done.
Reviewer #1 - Other Suggestions: Please use CORTICOSTEROID throughout. **Reviewer #2 - Other Suggestions:** The references in the Introduction do not match with the text, and should be meticulously checked: - Reference 1 cannot be accessed from the internet - The following link may be added for access to reference 3 www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf - Reference 4? - Reference 5 does not provide the information needed. I would replace it by reference Hekking et al J Allergy Clin Immunol. 2015 Apr;135(4):896-902 - Reference 6 is not about impact of severe asthma on individuals' quality of life - Reference 7 is not about costs of *severe* asthma, but costs of *uncontrolled* asthma. - Reference 7 is not about "novel therapies" - Reference 8 does not provide information on costs of severe asthma	**Re: Reviewer #1:** Done **Re: Reviewer #2:** - Ref 1 seems to be working - Link was added - Ref 4 was fixed - Ref 5 - The reference I put match the one indicated by the author of the section. If you all agree I can switch around ref 5-6-7-8.
Page 8: - the treatment of Churg Strauss Syndrome is much more complex than "low dose oral corticosteroids". This should be nuanced.	We agree. This sentence has been revised to: *"Churg Strauss Syndrome (CSS) and allergic bronchopulmonary aspergillosis (ABPA) occur in a minority of individuals with severe asthma, but recognition of these syndromes is important as they may dictate additional treatment requirements, such as oral corticosteroids and anti-fungal treatment."*
Page 8 (top): - one might consider HR-CT scan to exclude alternative diagnosis mimicking severe asthma, such as bronchiectasis - Reference 16 may be replaced by a more recent one: Sullivan PW, Ghushchyan VH, Globe G, Schatz M. J Allergy Clin Immunol. 2017 Apr 27 (e-pub).	- We agree and have added this sentence, which aligns nicely with the diagnostic algorithm. - This cannot be included because it was published after March 10, 2017 which is beyond the cut-off date for our literature search.
Page 10 (biomarkers): - reference 23 is not the correct one (should be ref 26 by Simpson et al) , and the figures on eosinophils and neutrophils are, I believe, not correct either	Thank for you reviewing the references so carefully. The reference and percentages have been corrected and an additional comment and reference has been provided to explain the origin of the 3% cut-off for eosinophilia
Page 10 - reference 27 should better be replaced by Veen et al: Consistency of sputum eosinophilia in difficult-to-treat asthma: a 5-year follow-up study. J Allergy Clin Immunol. 2009 Sep;124(3):615-7 - references 28, 29 and 30 are out-dated. They should be replaced by the more recent Phase III trials: Ortega et al	- Ref 27 has been replaced as suggested. - The original studies referenced have been updated to the more current studies suggested.

NEJM 2014, and Bel et al NEJM 2014, Castro Lancet Respir Med 2015 - Reference 31 should be completed in the reference list: Gibson et al. Lancet. 2017 Aug 12;390(10095):659-668 - Sputum eosinophils have been used to predict the response to IL-5 therapy, but peripheral blood eosinophil counts are better predictors of response (see also page 11). This should be briefly mentioned in the text here. - FeNO, 2nd paragraph. Maybe I missed it, but I cannot find data in reference 34 showing that outcomes of omalizumab therapy did not differ according to the level of baseline FeNO - Reference 36 is not accessible - bottom: A reference is missing for the trial that concluded that subjects with blood eosinophil counts ≤200/µL receiving azithromycin experienced fewer severe exacerbations than subjects with blood eosinophil count >200 /µL	- Included as a new reference as the abstract was received pre March 2017 (lit search cut-off) - Agree with this comment and this has been added to the text "blood eosinophils are a more consistent predictor of response to anti-IL5 medications." - The data on FeNo was included in the supplementary appendix. - Ref 36 seems to be working - Added the reference.
Page 11. When referring to post hoc analysis of the SIROCCO and CALIMA studies, it would be helpful to mention that these were trials with benralizumab	Revised to include this information.
Page 11. The paragraph on azithromycin should be rewritten, given the new evidence from the recent AMAZES study (Gibson P. et al, Lancet 2017)	Included as a new reference as the abstract was received pre March 2017 (lit search cut-off)
Page 13; - LAMA in severe asthma; efficacy in adults: the first 10 lines are not dealing with severe asthma; these can be skipped.	This section has been edited to only include data on severe asthma.
Page 15: - The macrolide section should be updated in view of the recent AMAZES trial (ref 31, Gibson et al, Lancet 2017). - I would skip the parapgraphs on troleandomycin and the MARS trial, because it does not provide information that is relevant to clinical practice.	- Included as a new reference as the abstract was received pre March 2017 (lit search cut-off) - The data on troleandomycin was retained as these are the only trials examining the endpoint of oral corticosteroid reduction. The MARS trial was also included as it is useful for readers to know that this trial was attempted, however, the details have been removed.
PICO 5 - The key messages may be formulated in a more concise way (details belong in text, not in key messages) - Key message 1: 2nd line superfluous (is included in the definition of severe asthma) - key message 3: has already been covered in section 2	- Agree that we can remove the second line of key message 1. Although slightly redundant to the key message in section 2, it was kept in this section for readers to be able to have all of the known predictors of response to omalizumab (biomarkers and clinical characteristics) in one key message.

Page 23 & 24; - Comparison of anti-IL5 therapies: One recent study by Mukherjee M et al Am J Respir Crit Care Med 2017 (in press) showed that weight-adjusted IV reslizumab was superior to fixed-dose SC mepolizumab in attenuating airway eosinophilia in prednisone-dependent asthmatics, with associated improvement in asthma control. Add to text?	- Unfortunately, evidence published or in press after our lit search cut off dates is not able to be cited. This has been 'accommodated' in the 'gaps' section instead on page 27.
- Conclusions: line 2-4 "In addition ….therapies" is superfluous because it is included in the definition of severe asthma.	- This was included here to emphasize the importance, but we acknowledge the repetition and have removed it from this conclusion.
- Conclusions: Not only previous exacerbations are key for treatment success with anti-IL-5s but also chronic oral corticosteroid dependency. Important to note is that blood eosinophils may be reduced by oral corticosteroid treatment, which implies that eosinophilia may only emerge after oral steroid-tapering.	- We disagree with the first statement. Chronic oral CS dependency was not an inclusion criteria in the large clinical trials, and the number of CS dependent patients was either low or none. Furthermore, the benefit was present in non-CS dependent patients. In contrast, exacerbations was an inclusion criteria for all. - We agree with the last point, and have added 2 sentences to the phenotyping section on page 9: *"Recent or chronic use of medications such as oral corticosteroids that may affect biomarkers should be taken in to consideration when phenotyping patients. For example, if peripheral eosinophils are normal in an individual on chronic oral CS, consideration should be given to tapering the CS and repeating the biomarker."*
Reviewer #4 – CRGC There is no appendix 1. I anticipate that the evidence tables will be online. Suggest the web link be inserted here.	Yes, it will be available online.
Page 5: suggest add a heading above the first paragraph in the box "severe asthma" to highlight that this is the definition of severe asthma and what follows is the definition of uncontrolled asthma.	Yes
Page 5: #4. May be clearer for the reader to modify this to read prebronchodilator FEV1 rather than "after appropriate bronchodilator withhold"	I think this is likely phrased like this based on the potential inability to withhold bronchodilator and thus should leave as is.
Page 7: in the paragraph that begins with "more specialized investigations" the second sentence could be modified to enhance clarity for the reader. I am referring to the sentence "In particular, comorbidity should be considered during the preliminary assessment if there is a lack of response to ICS combined with at least one other controller, despite the assessment and usual management of most frequent reasons for poor control."	Added the following at the end of the sentence: - i.e. inhaler technique and adherence.
Page 8: Box1 #4. Suggest remove the word "again".	Not required in case initial modification of therapy has not worked.
Page 10: para 2 - sputum neutrophilia by definition requires, in addition to a high percentage, an increased total cell count. Suggest add language that includes neutrophils greater than 67% and total cell count of greater than $9.7x10^6$ per gram.	Changed It should be noted these values are in the context of total cell counts including neutrophils greater than 67% and total cell count of greater than $9.7x10^6$ per gram.
Page 11: para on total IgE – suggest change mucous to mucus.	Done

Page 12: para 1: suggest modify the second sentence to enhance clarity for the reader as follows. "Periostin does not appear to be a useful biomarker in childhood asthma because periostin levels are normally high in growing children…"	Done
Page 13 - last paragraph discussing efficacy in adolescent and pediatric individuals. The authors describe an improvement in FEV1 by 100 mils as "modest". This increase in FEV1 in this population sounds large to me. Suggest review and revise if necessary.	Leave as is.
Page 16 and Fig 1: Suggest capitalize Mycobacterium. On the figure 1, one instance is capitalized one is not. On page 16 in the safety section lowercase is used.	Okay.
Page 18 in the section on "medication use" in the second paragraph the study is cited where an objective was to withdraw inhaled corticosteroids. Do the authors want to add a qualifier here that indicates to the reader that withdrawal of inhaled corticosteroids is not a clinical goal in the use of biologic therapy.	I think it is appropriate not to put this qualifier as if a person is on very high doses of ICS a reduction would be clinically useful especially in children.
Page 18 in the section on efficacy in adolescent and pediatric individuals. The automatic formatting of reference 19 and 31 appears to have failed.	Okay
Page 18 in the paragraph that begins with "Omalizumab was associated with a significant reduction in the rate of…" There is a typographical error. Suggest replace the word fall with the word all	Fall in terms of season but rephrased. (on page 19 now)
Page 19 in the section on safety there are two sentences excerpted below… " There was no difference in asthma related mortality between omalizumab and placebo in asthma. An incidence of at least 0.2% is reported in the product monograph based upon spontaneous reports." I read the flow of this as indicating a risk of death of 0.2%. Is this the risk of anaphylaxis? Please review and modify as appropriate.	Rephrased Yes – added anaphylaxis
Page 23 Benralizumab Safety: this side effect profile is outlined but not compared to placebo. For the other Biologics this side effect profile is compared to placebo. Do you have this information to add?	Added the following sentence: Overall there was no appreciable difference in side effects between active and placebo treatment groups.
Page 24 Conclusions section: In PICO2 sputum is suggested as a biomarker that predicts response to Biologics but it is not mentioned here in the conclusion section of pico five as a biomarker. Do the authors wish to add a statement here?	The following sentence was added: Sputum eosinophilia, although limited by availability, also predicts response to anti IL 5 therapies.
Gen. comment: Theophylline – Would the authors agree that it is time for theophylline to find its way into the clinical practice guidelines history book. As a practicing respirologist personally I have not written a prescription for theophylline in the past 10 or more years. For a guideline based on the Canadian perspective,	Agree limited use but appropriate to leave for N of one trials and also a Lancet paper showing withdrawal of theophylline in asthma to be associated with worse outcomes. Peter Barnes was a co-author.

I would recommend the authors consider removing theophylline from the guidelines.	
Gen. comment: Death: I understand that death is an important safety outcome. The risk of death is systematically dealt with in the review of Tio and of each of the Biologics in the manuscript. Reflecting on the message, I wonder if the reader may be left with the impression that the risk of death in the use of these medications is an important consideration when deciding whether to implement therapy when it is in fact a rare occurrence. I would ask that the authors consider this comment and consider adding a statement or edit the manuscript to mitigate this impression. The description of deaths associated with Benralizumab stands out in particular and including this preliminary data in a position statement may impact the future use of a promising new biologic.	I do not think we imply the deaths are related to the medications but that in the context of any new treatments the occurrence of a death should be highlighted and in this context it not being associated with the medication.
Gen. comment: Tiotroprium and inflammation: the authors have done a thorough job evaluating this medication and the Biologics and have indicated that there are no comparative studies. Similarly there is a thoughtful discussion around relative costs. As a practicing Respirologist, I would not add to tio in a patient with ongoing eosinophilic airways inflammation as a first choice when there are Biologics that could address the inflammation. In the absence of comparative studies but based on the emphasis in this guideline on phenotyping for severe asthma do the authors wish to add a statement to the discussion that would clarify an approach such as this?	There are cost implications and the pragmatic clinical situation is that tiotropium offers a potential 21% reduction in exacerbations at a much lower cost.