Answering Reviewers:

Number ID 03317263.

Dear Colleague, thank you very much for the reviewing our manuscript, your conclusion and comments. Your comments are very important to us. Let me provide responses.

1. Would like to know more about the interval between symptoms and exploration of reflux?

Only 3 out of 37 patients with EA did not experience any symptoms during pH-impedance monitoring. Before pH-impedance testing their parents spontaneously reported extraesophageal symptoms (cough and recurrent bronchitis). Thirty four patients reported symptoms during pH-impedance testing. Positive symptom association was defined in children who had a symptom association probability (SAP) over 95%. SAP was positive in 3/20 (15%) in the EA with GERD group and in 8/17 (47.06%) in the EA without GERD group. The most frequently reported symptom for the EA patients was cough in both groups.

In Belarus, a national follow-up program for EA patients has not yet been developed. So, these patients come to our clinic for examination when they have symptoms. Some of them did not experience any symptoms during pH-impedance monitoring.

2. Discuss please any correlation also with severity and therapy.

It's really good idea, but we didn't set the aim of this work to correlate the severity of GERD and therapy.

We have these results about therapy in our patients. 8 children in the EA with GERD group (40%) and 9 children in the EA without GERD group (52.9%) had previously been treated with proton pump inhibitors (1-3 months ago). After therapy, clinical improvement was observed only in 47.05% of patients

in both EA groups received therapy. PPIs therapy was discontinued in all patients for at least 7 d before the impedance-pH testing.

3. The subtitle national cohort study seems very ambitious: was this indeed a national study?
It's very important suggestion. In Belarus, a national follow-up program for EA patients has not yet been developed. We examine patients who contacted us with any disturbances symptoms. This study was designed to assess clinical symptoms and pH-impedance data in children after EA open surgical repair in order to provide data that will support development of a national program for the follow-up of EA patients.
And for this reason we decided to change the title of our manuscript "Gastroesophageal reflux disease in pediatric esophageal atresia: assesment of clinical symptoms and pH-impedance data". We really didn't examine and follow-up the majority of EA patients in our country.

Number ID 03832032

Dear Colleague, thank you very much for the detailed and constructive reviewing our manuscript, your conclusion, suggestions and comments. Your comments are very important. Let me provide responses.

1. In general, I'd concentrate the paper more on symptoms and the underlying pH-metry.
We decided to change the title of our manuscript "Gastroesophageal reflux disease in pediatric esophageal atresia: assesment of clinical symptoms and pH-impedance data" because we really didn't examine and follow-up the majority of EA patients in our country and provide the information mostly about symptoms and pH-impedance data.

2. Why is the follow-up necessary when patients don't have symptoms?

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)-North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Guideline (2016) recommends that patients with EA should be evaluated regularly by a multidisciplinary team including pulmonology, gastroenterology and otolaryngology, even in the absence of symptoms. Monitoring of GERD (impedance/pH-metry and/or endoscopy) should perfom in all EA patients (including asymptomatic patients) at time of anti-acid treatment and during long-term follow-up. Therefore, according Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, 2018, recommends monitoring GERD at time of-PPIs even in asymptomatic children, to confirm the absence or the persistence of reflux disease, and the need to continue treatment.The main goal of pH impedance testing is not to diagnose pathology but rather to try to correlate symptoms with reflux events.

In Belarus, a national follow-up program for EA patients has not yet been developed. So, we follow the recommendations of the above guidelines and work in order to develop our follow-up program.

3. What is the incidence of Barretts'esophagus or carcinoma after AE?

The incidence of esophagitis and esophageal gastric and intestinal metaplasia (Barrett) is increased in adults with EA as compared with the general population according data of ESPGHAN-NASPGHAN Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Esophageal Atresia-Tracheoesophageal Fistula (2016). Several studies have shown no increase incidence of esophageal cancer (adenocarcinoma, squamous cell carcinoma) in adults with EA, esophageal cancer remains a concern.

We haven't our own data about the incidence of Barretts'esophagus or carcinoma after AE.

4. Remove the description of your hospital. National single-center study: a little bit confusing.
Sorry for the description of our hospital. We only describe that all EA children were operated on in the Department of Pediatric Surgery of The National Centre of Pediatric Surgery, and point that it serves a pediatric population (up to 18 years of age).

5. Prospective study: recorded in clinical trials? Or retrospectively analyzed?
This study was a retrospective chart review done in The National Centre of Pediatric Surgery and registered at The National Centre of Pediatric Surgery trial registry. All children were operated on and then treated in the Department of Pediatric Surgery of The National Centre of Pediatric Surgery. All EA open surgical repair patients, aged 1-18 years, who were bothered with troublesome symptoms and who have contacted our clinic for the last 3 years, was examined using combined impedance-pH testing and upper gastrointestinal endoscopy (with histological study of biopsied mucosa samples). At the same time, we retrospectively evaluated 66 patients with proven GERD (acid exposure time > 7%, total number of retrograde bolus movement > 70), sex- and age-matched to the EA group, who were enrolled in the study to serve as a control group. The research was carried out at a single institution, and it was a retrospective study. Further accumulation of study data is needed for a better comparrison of data in EA with GERD patients and patients with GERD with nonoperative esophagus. Surely, these data should be evaluated and confirmed with a prospective multicenter study.

6. The surgical procedures need an accurate description? Were there any gastric/colonic pull-ups?

All patients had their repair done by thoracotomy in early postnatal period (days 1-2), with primary direct anastomosis of esophagus "end to end". There were no cases of gastric/colonic pull-ups in the group of studied EA patients. Patients were excluded according to esophageal replacement therapy (gastric pull-up, jejunal/colonic interposition) and receipt of fundoplication.

7. We need the time interval from operation to follow-up I have a hard time understanding how children let's say <5y express their GERD symptoms. This might explain why coughing is one of the foremost symptoms.
In all patients detailed clinical history and parental reported symptoms in all patients were analyzed. Symptoms in study groups were recorded during the study as events and by means of a questionnaire prepared specifically for this study for patients with GERD-related symptoms. We ask parents of children (usually younger 8 years) to fill out this questionnaire, so we can see what worries parents of children who cannot explain the symptoms that bother them. Thus, one of the most common symptoms in children younger 5-6 years old are the symptoms noted by their parents, such as coughing, vomiting, feeding difficulties, recurrent bronchitis and pneumonia. Evaluation of the patient's and/or parental questionnaires showed that the most frequently observed symptom in EA patients with GERD and without GERD in our groups was cough.
In addition, only those EA patients who treated with troublesome symptoms after applying the exlusion criteria and who have contacted our clinic over the past three years was included in this study.

8. Further, there is a huge inclusion bias towards patients with symptoms. We have a large percentage of patients with symptoms because we examined patients who come to our clinic for examination when they have symptoms that disturbed them. This was the main reason for their examinationusing pH-impedance testing and upper GI endoscopy with biopsy. We haven't a

national follow-up program for EA patients, so we examine majority patients with symptoms.

9. pH-metry in patients is not an easy thing to do, not even touching the financial problems. Why did'nt you perform manometry? This would bring additional valuable information I think would help clarify your results.
The results and additional information obtained performing ESO manometry is really valuable. But there are no guidelines for performing esophageal manometry in pediatric patients and interpreting the results obtained in children, only Chicago classification, and we perform high-resolution esophageal manometry according to it. One more, we perform ESO manometry without sedation in our patients, so this procedure seems to us more difficult to carry out. In our studying groups there is only a small group of patients who underwent high resolution esophageal manometry, so we decided not to show these results.

10. I'm not really sure if you can MNBI as parameter as it is measured at a different location in all patients.
We determined distal MNBI in all patients at the same distance depending on age (from 1 year to 10 years - 3 cm above the lower esophageal sphincter, older than 10 years - 5 cm above the lower esophageal sphincter) and calculated when neither reflux episodes or swallowing were present. So we decided to propose our data about this parameter that we expect will be really interesting and valuable for the future research purposes.

11. I'm quite sure that gastroparesis has a huge effect (after expected vagotomy), did you test for that?
According to exclusion criteria and the clinic of our patients we excluded this diagnosis. Gastroparesis usually is the complication of the early postoperative period, but we examined EA patients in our groups at age > 1 year. We have never meet gastroparesis in our patients age >1 year.Besides we performed

upper GI barium contrast study to exclude mechanical obstruction and another pathology. But we didn't perform examination using Smartpill capsules.

12. Is NMBI correlated with future metaplasia?
We have no data about correlation the values distal MNBI with future metaplasia as well with another esophageal pathology. However, it's great research interest in the future. But it takes time to see this correlation.

13. Discuss LPR.
One more limitation of our study is the inability to rule out laryngopharyngeal reflux (LPR), because we use probes with one pH-sensor located in the distal part of the probe. This group of patients commonly complain of throat issues, such as chronic cough, throat clearing, or sore throat. Some of our patients had similar complaints. The most common tests in these patients suspected of reflux-related laryngeal symptoms or LPR are endoscopy and pH monitoring. But these tests have poor sensitivity. The most popular examination of this pathology is proximal or hypo-pharyngeal pH monitoring, but these 2 probes have sensitivities of only 40—50% at best, limiting their utility. Thus, there is a need for a better test with increased sensitivity for patients suspected of having LPR. One more we didn't perform salivary pepsin testing.

14. Actually, please confer Brant Oelschlagers study about Fundoplication in Annals of Surgery around 2015, and relate more to those figures.
Thank you very much for the suggestion so interesting study. We carefully studied this article. But our exclusion criteria are the next: receipt of fundoplication in EA patients and history of any abdominal surgery in control group; and for all patients age<18.