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Definition of sinonasal and otologic exacerbation in patients with primary ciliary dyskinesia - an expert consensus

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Abstract

Background: Recurrent infections of the nose, sinuses, and ears are common problems for people with primary ciliary dyskinesia (PCD). While pulmonary exacerbations in PCD are defined, there is no definition for Ear-Nose-Throat (ENT) exacerbations, a potential outcome for research and clinical trials.

Methods: We set up an expert panel of 24 ENT specialists, respiratory physicians, other healthcare professionals, and patients to develop consensus definitions of sinonasal and otologic exacerbations in children and adults with PCD for research settings. We reviewed the literature and used a modified Delphi approach with four electronic surveys.

Results: Both definitions are based on a combination of major and minor criteria, requiring three major or two major and at least two minor criteria each. Major criteria for a sinonasal exacerbation are: 1) reported acute increase in nasal discharge or change in colour; 2) reported acute pain or sensitivity in the sinus regions; 3) mucopurulent discharge on examination. Minor criteria include: reported symptoms; examination signs; doctor´s decision to treat; improvement after at least 14-days. Major criteria for the otologic exacerbation are: 1) reported acute ear pain or sensitivity, 2) reported acute ear discharge, 3) ear discharge on examination, 4) signs of otitis media in otoscopy. Minor criteria are: reported acute hearing problems; signs of acute complication; doctor´s decision to treat.

Conclusion: These definitions might offer a useful outcome measure for PCD research in different settings. They should be validated in future studies and trials together with other potential outcomes, to assess their usability.

246/250

Introduction

Dysfunction of motile cilia due to genetic mutations leads to a wide range of symptoms including multiple organ systems in patients with primary ciliary dyskinesia (PCD).[1, 2] Despite the clinical heterogeneity, the greatest impact of impaired mucociliary clearance is seen on the respiratory tract and the ears.[3] Patients present with persistent wet cough and recurrent lower airway infections, progressing with time to irreversible lung damage.[3] Inadequate clearance of mucus, pathogens, and debris in the nose and sinuses, as well as in the eustachian tube and middle ear, leads to bacteria growing in the mucus-clogged airways. Consequently, patients experience recurrent episodes of sinonasal infections, and the risk of sinonasal disease increases with age, with chronic rhinosinusitis (CRS) becoming a common feature as disease progresses.[4–6] From the ears, recurrent episodes of acute otitis media (AOM) often progress to severe bilateral otitis media with effusion (OME) and conductive hearing impairment.[7–11] Acute infections of the nose, sinuses, and ears in PCD, usually involve already impaired upper airways, with a more complicated pathophysiology and course compared to common acute upper airway infections. Respiratory exacerbations are a significant determinant of morbidity and subsequent care requirements of people with chronic respiratory diseases. They are typically characterised by deterioration of the patient´s clinical condition, most often due to viral or bacterial infections or exposure to other triggering factors. Exacerbations often require additional management and have significant effects on disease progression, severity, and patients´ quality of life.[12–15] For clinical and epidemiological research, exacerbations are important outcomes, in measuring burden of disease or response to treatments.[16, 17] Despite their importance, there is a lack of evidence on the frequency of exacerbations - pulmonary, sinonasal, and otologic- among people with PCD, and their impact on quality of life has not been measured. Lack of evidence is partly explained from the lack of precise definitions. Pulmonary exacerbations have been defined, and were recently included in a core outcome set for pulmonary disease interventions,[18, 19] in the framework of the BEAT-PCD clinical research collaboration supported by the European Respiratory Society (ERS).[20, 21] The existing definition excluded upper respiratory tract exacerbations because they often occur independently from lower respiratory tract exacerbations and have different prognosis.[18] Therefore, despite their impact on severity of PCD, there is still no definition for Ear-Nose-Throat (ENT) exacerbations. This lack of definition is an important gap for future clinical

research in the field, particularly because clinical outcomes capturing ENT disease in PCD are even fewer than the ones available for lung disease.[22]

Using an international panel of specialists involved in PCD care, we aimed to develop a consensus definition of ENT exacerbations for children and adults with PCD, participating in clinical research.

Methods

Participants and purpose of the consensus

We established an expert panel consisting mainly of ENT specialists, with expertise in managing children and adults with PCD. Experts participated in the panel by invitation from the study co-ordinators. We invited specialists from PCD reference centres in Europe, particularly centres participating in the EPIC-PCD study. We also contacted PCD reference centres internationally and requested for contact details of ENT specialists with expertise in PCD who might be interested to join the panel. We encouraged invited participants to suggest further members ensuring wide international representation, resulting in participating ENT specialists from Europe, Canada, Australia, and Japan (Supplementary Table S1). Additionally, we invited a paediatric and an adult pulmonologist, involved in the consensus group of the pulmonary exacerbations definition,[18] and other healthcare professionals involved in PCD patient care and research. The panel was completed by two patient representatives, an adult with PCD and a parent of a child with PCD; 24 members in total, representing 13 countries. To ensure significant patient involvement and input from the people who experience first-hand these exacerbations, we also set up a parallel group of patient and parent volunteers, with support from the European Lung Foundation (ELF),[23] who did not join the consensus panel, but provided feedback and were encouraged to participate in the surveys. The activities of the panel and the patient group were coordinated by two facilitators, a clinical epidemiologist with expertise in PCD research (MG) and a PCD PhD candidate (YTL); the latter did not participate in voting. An initial virtual panel meeting refined the aims and proposed methodology. It was concluded that standardised definitions for PCD were missing and decided unanimously to produce two separate definitions: one for sinonasal exacerbations and one for otologic exacerbations. Our goal was to establish definitions meant to be used in research and clinical practice.

Literature search

We conducted a systematic literature search of publications referring to ENT exacerbations in patients with PCD, or separately sinonasal and otologic exacerbations. Given the anticipated limited pre-existing literature on the topic, our search strategy was expanded at the outset to include other areas with common characteristics, in particular CRS. We searched PubMed for studies published between January 2012 and December 2021 using the following keywords: ciliary dyskinesia, primary OR immotile cilia syndrome OR Kartagener/ AND exacerbat* OR infect* OR acute/ AND sinus* for sinonasal exacerbations, or otit* OR ear or otol*, for otologic ones. We simplified the terms, excluding PCD specific keywords, to expand on other diseases excluding the PCD related keywords. We did not exclude any publication type or language.

Reaching a consensus

A modified Delphi approach with online (eDelphi) surveys was used. Initial literature search results revealed that identified pre-existing definitions did not cover the need for PCD-specific definitions but should be used as a starting point for the first eDelphi survey. Based on these definitions and the panel consensus, we identified important components for definitions of sinonasal and otologic exacerbations. For each survey, participants received detailed instructions and a link via e-mail, then two reminders to respond within two and three weeks.

The panel decided that at least an 85% response rate would be required to proceed to the next survey and that 80% of agreement would signify consensus; however, possibility of accepting lower agreement as consensus was left open provided that the panel would be informed and there would be no veto against it. Each survey (eDelphi survey Supplementary material 1-4) included different types of questions to reach consensus initially on the included components for each definition and subsequently on the details of specific components e.g. elements of included components such as specific symptoms or signs. Each survey was designed based on the results of the previous survey and included a summary of these for the panel´s information. Participants were asked to explain their opinions in free text boxes, particularly where consensus was not achievable despite high agreement, so statements could be clarified and modified in the next round. The number of surveys was not predefined, but ultimately 4 surveys were required. A virtual meeting was organised with MG and the patient group to explain details of the project to the patient or parent members and provide any answers to their questions. Replies remained anonymous to the

panel and only the facilitators had access to identifying information. After the eDelphi surveys were completed, the results of the final survey were circulated among the panel to ensure all members agreed with the final definitions.

Results

Literature search

Our search resulted in total of 2352 abstracts related to sinonasal and 2208 to otologic exacerbations respectively. No abstracts with definitions specific to PCD were identified. After excluding duplicates and screening the abstracts, we identified 24 manuscripts that referred to sinonasal exacerbations. By searching their references 6 additional manuscripts were identified, 30 in total, including one systematic review.[24] A summary of definitions used in literature for sinonasal exacerbation in patients with CRS in the identified studies is presented in Table 1.[24–53] These definitions were discussed at a virtual expert panel meeting and the elements they used were considered for developing the initial survey. No study fulfilled the criteria of otologic exacerbation of a chronic condition.

eDelphi surveys

Response rates to the eDelphi surveys ranged between 88 and 100% (Supplementary Table S1). In addition, two to five members of the patient group completed each survey. In survey 1, the panel assessed opinions about the importance of sinonasal and otologic exacerbations for people with PCD and components that should be included in the exacerbation definitions. Consensus was reached that exacerbations from the nose and sinuses are an important problem for both adults and children with PCD, they impact the quality of life of people with PCD and can be an important outcome measure for ENT clinical trials in PCD. For otologic exacerbations, opinions were similar, however no consensus was reached on the importance of this problem for adults with PCD, primarily due to smaller frequency of acute ear exacerbations in adulthood. The panel also agreed that sinonasal, otologic, and pulmonary exacerbations may occur separately from each other, highlighting again the importance of separate definitions. Responses to key questions about the components of the two definitions are presented in Supplementary Table S2. The combination of new symptoms or worsening of baseline symptoms and of new clinical signs or changes in clinical examination was voted as the best combination of components to define both sinonasal (93%) and otologic (97%) exacerbations. No consensus was reached

about including the following components: 1) changes in imaging for sinonasal exacerbations, 2) decision of ENT specialist to treat (for both definitions), and 3) complete resolution of any changes and return to baseline (for both definitions).

Survey 2 included questions on specific elements, particularly symptoms (Supplementary Table S3) and signs (Supplementary Table S4) for the sinonasal and the otologic exacerbation definitions. Agreement was reached for three symptoms and two signs for each definition in this round. Items that achieved 60-79% agreement in survey 2 were discussed again in survey 3. Tables 2 and 3 follow the process of reaching a consensus for the two definitions step by step from survey 2 to survey 4 and the levels of agreement until consensus was reached, or not. Survey 2 also clarified that sinus imaging should not be an absolute requirement for the definition of a sinonasal exacerbation, with main reasoning that it should be restricted for baseline assessment and for complications, and that it entails too much radiation and offers little in case of acute exacerbations (85% agreement).

Survey 3 discussed elements from previous surveys, which had scored highly but not yet reached a consensus on inclusion (Supplementary Table S5). The panel unanimously agreed in this survey to introduce major and minor criteria for both definitions. This was already discussed as a possibility at the first panel meeting and was raised again at this point of the project, suggesting considering the most important criteria as major and the rest as minor, according to the level of agreement reached for each. We also reached consent (85%) that all clinical signs or changes seen in clinical examinations included in both definitions should be assessed in relation to previous examinations. In survey 4, participants voted specifically about major and minor criteria. For criteria for which consensus (≥80% agreement) was already reached, the panel was asked to vote whether they should be included as major or as minor (Tables 2 and 3). Criteria that reached more than 50% but less than 80% agreement in survey 3, were now voted upon including as minor or excluding from the definitions.

Based on discussions that clinical practice may differ substantially from research practices, particularly in the non-PCD ENT specialist, although we originally considered that the definitions would cover also clinical practice, the panel decided (100% agreement) to include the following clarification: “These definitions are aimed to be used in research settings, especially in clinical trials, to define a sinonasal or otologic exacerbation in patients with PCD”. The panel also agreed that a) 3 major or b) 2 major and at least 2 minor criteria are needed to define a sinonasal or otologic exacerbation (Table 4). Panel members were

invited to submit alternative proposals in case of disagreement; no other proposals were submitted. For sinonasal exacerbation, we reached consensus on three major (reported acute increase in nasal discharge or change in discharge colour, reported acute pain or sensitivity in the sinus region, and mucopurulent nasal discharge at examination) and six minor criteria (reported acute blocked nose or worsening in chronic feeling of blocked nose, reported acute decreased sense of smell, increased mucus production or postnasal drip at examination, signs of acute complication at examination, doctor´s decision to treat, and important improvement in symptoms or clinical findings after a period of at least 14 days). For an otologic exacerbation, we reached consensus on 4 major (reported acute ear sensitivity or pain, reported acute ear discharge, ear discharge at examination, and sign of otitis media in otoscopy) and 3 minor (reported acute hearing problems/worsening in preexisting hearing problems, signs of acute complications at examination, and doctor's decision to treat). Major criteria were decided on at least 80% consensus and minor on at least 74%, which was agreed in the panel (Tables 2 and 3). Lastly, the panel highlighted that no criterion was an absolute requirement for either definition (Table 4).

Discussion

An international panel of ENT specialists, pulmonologists, healthcare professionals, and people with PCD, agreed on consensus definitions of sinonasal and otologic exacerbations in children and adults with PCD to be used in research, especially in clinical trials. This effort followed similar approach to the one used to develop a consensus definition of pulmonary exacerbations in PCD.[18] Although upper and lower airway disease in PCD should be managed holistically and exacerbations often occur simultaneously, or progress to involve the whole airways, our panel agreed that exacerbations from the nose, the sinuses, and the ears require separate definitions.[54] They can occur individually and have different characteristics. Both are an important problem in children with PCD and whilst in adults sinonasal exacerbations remain a major issue, otologic exacerbations are less common.

Main strengths of the study were the international and multidisciplinary nature of the panel, and the inclusion of patients and parents of children with PCD, together with the added group of patient volunteers. We performed a thorough systematic review of the literature, expanding our search also to other conditions, such as other types of CRS, which have similarities with PCD. We retained a high panel response rate throughout the study. Although the panel considered originally developing definitions that would also be used for clinical practice, we agreed during the process that this would not be feasible. Clinical outcome measures for research, even simple ones as these definitions, need to be very clearly defined, while for clinical practice a decision for an exacerbation might be needed to be taken only based on reported symptoms, often without any examination, requiring sometimes a less precise definition.

Our panel discussed thoroughly whether existing definitions specifically for exacerbation of CRS, could be used also for children and adults with PCD, without the need to develop disease-specific definitions. We considered all available definitions (Table 1), particularly the latest European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) that defined acute exacerbation of CRS as worsening of symptom intensity with return to baseline CRS symptom intensity, often after intervention with corticosteroids and or antibiotics.[36] We reached consensus that none of them fully covered the purpose of a PCD-specific definition, although

they highlighted important components which we then discussed. Most of the available definitions were not precise enough to be used as outcome measures for clinical trials and refer to deterioration of symptoms in general without listing specific symptoms. Considering that patients with PCD grow accustomed to their chronic symptoms and tend to underestimate them, we aimed to refer to specific symptoms. The panel members agreed also on the need to include in the definition PCD-specific signs seen at simple examination, which was not part of most existing definitions. We found no eligible definitions that could be used as a starting point for otologic exacerbations.

Throughout the process, our panel highlighted the need to select elements which could be assessed easily, in different settings and would not require complex ENT examination or a specialist with expertise in PCD to assess them. Most criteria refer to symptoms, or signs that can be observed in simple clinical examination, the most complex assessment included being otoscopy. Panel members agreed that patients with PCD often underestimate their upper airway symptoms, which are non-specific and to which they grown accustomed over time, highlighting the need to also consider simple signs in the definitions.[4, 7, 55, 56] This was also shown in a recent study from the ENT Prospective International Cohort of PCD Patients (EPIC-PCD) that reported a lack of correlation between sinonasal and otologic symptoms with objective measurements.[57, 58]

Two components that required long discussions and voting rounds were doctor's decision to treat and the need for improvement of the symptoms and signs. In both definitions, decision to treat was included as minor criterion since it could occur regardless of an exacerbation (e.g. detection of Pseudomonas aeruginosa in a routine nasal or ear sample). The panel clarified that treatment should not only refer to need for antibiotics but also other medication or management practices such as upper airway clearance, e.g. start or increased frequency of saline irrigation. Return to baseline was a term that was not found agreeable to most panel members. Even though improvement in symptoms and signs, where follow-up examination is possible, was included as a minor criterion for the sinonasal definition, participants agreed that it is difficult to measure improvement as deterioration is partly expected due to the chronic

nature of the disease. In case of acute ear exacerbations especially, this was not considered possible, and it was not included at all in the definition.

This initiative was developed in the framework of the BEAT-PCD ERS clinical research collaboration (https://beat-pcd.squarespace.com), as part of our efforts to define and promote the use of reliable clinical outcome measures for PCD trial and clinical research. [20] Evidence-base for PCD treatment is small, and there are no trials which have accessed specifically management of the upper airways. Identifying the most suitable clinical and patient-reported outcomes to be used as endpoints focused on the upper and lower airways, was one of the top priorities related to PCD research identified recently by experts in the field. These new definitions were developed to address a gap in disease-specific and relevant outcome measures for the upper airways. As more trials are needed to improve care of PCD and new potential therapies are in the pipeline, these definitions might offer a useful outcome measure in different research settings. It is important to use and validate them in future studies and trials, to assess their usability together with other potential outcomes.

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Author Contributions: M Goutaki and JF Papon developed the concept and designed the study. YT Lam performed the literature search. M Goutaki managed the study, designed the eDelphi surveys, analysed the data, and drafted the manuscript. All authors contributed to the surveys, interpreted results, and revised critically the manuscript. M Goutaki and JF Papon take final responsibility for all content.

Data availability: All data generated for this project was made available in the manuscript display items or supplementary information.

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Table 1: Summary of definitions used in literature for sinonasal exacerbation in patients with chronic rhinosinusitis

Definition	**References**
Acute increase in **severity** of sinus disease symptoms	Armbruster 2021
Sudden **worsening** of CRS symptoms with a **return** to baseline symptoms, often after **treatment**	Orlandi 2020; Bleier 2021
Acute worsening of pre-existing CRS symptoms with **subsequent return to baseline** symptoms **with or without endoscopic evidence**	Orlandi 2020; Makary 2021
Previous **diagnosis of CRS** exists, and a sudden worsening of symptoms occurs, with **a return to baseline symptoms following treatment**	Orlandi 2016; Philpott 2021; Wu 2019; Yan 2018; Barshak 2017
Presence of **purulence on endoscopy** during a symptomatic exacerbation of CRS	Orlandi 2016; Vandelaar 2019
Sudden **worsening of pre-existing** CRS symptoms is called a CRS exacerbation	Laulajainen-Honigsto 2020
Diagnosis of chronic rhinosinusitis and acute exacerbation of CRS according to the criteria described in the "European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)	Fokkens 2020; Yaniv 2020
Previous **diagnosis of CRS** but were experiencing **acute** exacerbation **of symptoms**	Fokkens 2012; Ghadersohi 2020; Kuiper 2018
Acute worsening of symptoms with return to baseline, often requiring a transient escalation in **treatment**, such as a course of oral antibiotics or corticosteroids	Fokkens 2012; Phillips 2019; Kuiper 2018; Phillips 2018
Acute exacerbation of CRS was defined as having received an a**ntibiotic** prescription **for worsening sinus symptoms**	Kwah 2020
Acute exacerbations among **surgically managed** CRS patients were defined as a post-endoscopic sinus surgery, after **90 days post-op**	Denneny 2018
Acute bacterial CRS exacerbations (**patient-reported** sinus **infections** and CRS-related **antibiotic use**)	Sedaghat 2018
Sudden **worsening of baseline** symptoms (or developing **new symptoms**) in a patient with an established CRS diagnosis	Lopatin 2018
Sudden worsening of the baseline CRS with either **worsening or new** symptoms. Typically, the acute (not chronic) symptoms **resolve completely** between exacerbations	Brook 2016
Worsening, with subsequent **resolution**, of symptoms in a patient carrying the **diagnosis of CRS**	Merkley 2015
Defined by minimum **SNOT-20** score of 1.0 on scale of 0 to 5	Jiang 2015
Worsening of symptoms: facial **pain** or pressure, nasal **obstruction**, nasal **discharge**	Rosenfeld 2015; Beswick 2020
Presence of **increased nasal congestion**, and **facial pain**; **increased sinonasal discharge**; usually presence of an unscheduled sick visit	Zemke 2019, Wu 2020

Acute exacerbation of CRS was defined in a patient in whom a previous diagnosis of CRS exists, and a **sudden worsening of symptoms** occurs, with a **return to baseline** symptoms **following treatment**	Orlandi 2016, Wu 2020
Natural exacerbation was defined as **patient-reported worsening of sinonasal symptoms** (i.e. runny nose, nasal congestion, and nasal obstruction)	Divekar 2015, Wu 2020
History of **sudden worsening of preexisting symptoms** suggests an acute exacerbation of CRS, which should be diagnosed by similar criteria and treated in a similar way to acute rhinosinusitis	Fokkens 2012, Wu 2020
Self-reported **medication use** (antibiotics and oral corticosteroids) for **worsened nasal and sinus symptoms**; self-reported **worsened purulence** in the past 4 weeks	Kuiper 2018, Wu 2020
Systemic **antibiotics**; systemic **corticosteroid**; plans for a **semi-urgent surgical intervention**; emergency department or **urgent care visit**, or a **hospitalization** for CRS	Wu 2020
Worse nasal symptoms	Wu 2020

CRS: chronic rhinosinusitis, SNOT-20: Sino-Nasal Outcome Test

Table 2: Process of reaching consensus for the items included in the definition of a sinonasal exacerbation.

	% of agreement			Included in the definition (% of agreement)
	Survey 2	**Survey 3**	**Survey 4**	
Patient-reported acute increase in nasal discharge or change in discharge colour	100	-	-	major criterion (100)
Patient-reported acute pain or sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead)	85	-	-	major criterion (83)
Patient-reported acute blocked nose or worsening in chronic feeling of blocked nose	92	-	-	minor criterion (78)
Patient-reported acute decreased sense of smell	69	58	74	minor criterion (74)
Reduced quality of life evaluated by any sinonasal specific quality of life questionnaire	73	50	61	not included
Mucopurulent nasal discharge at examination	100	-	-	major criterion (87)
Increased mucus production or postnasal drip at examination	92	-	-	minor criterion (70)
Signs of acute complication (e.g. orbital infection or abscess, meningitis, cerebral infection, cranial nerve palsy) at examination	72	52	83	minor criterion (83)
Acute frontonasal or maxillary tenderness at examination	-	-	65	not included
Doctor´s decision to treat, not necessarily with antibiotics but also with increased upper airway clearance or other medication		81	-	minor criterion (91)
Important improvement in symptoms reported by the patient or parent or in clinical findings in case further examination is possible, after a period of at least 14 days	-	80	-	minor criterion (74)

Items that reached ≥80% were automatically included in the definition. Items that achieved 60-79% agreement in Survey 2 were discussed again in Survey 3. Iter
that achieved 50-79% agreement in Survey 3 and newly suggested items by several members were discussed in Survey 4.
At Survey 4, members voted whether items should be considered as major or minor criterion or be included at all. We considered reaching consensus at ≥80% agreement for major criteria and ≥74% for minor criteria; items with <74% agreement were not included at all.

Table 3: Process of reaching consensus for the items included in the definition of an otologic exacerbation

	% of agreement			Included in the definition (% of agreement)
	Survey 2	**Survey 3**	**Survey 4**	
Patient-reported acute ear sensitivity or pain	92	-	-	major criterion (91)
Patient-reported acute ear discharge	92	-	-	major criterion (91)
Patient-reported acute hearing problems or worsening in preexisting hearing problems	85	-	-	minor criterion (74)
Reported feeling of fullness in the ears	77	58	57	not included
Ear discharge at examination	92	-		major criterion (83)
Signs of otitis media in otoscopy (i.e. erythema, collection)	92	-		major criterion (87)
Signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy) at examination	69	46	78	minor criterion (78)
Impaired hearing tested by pure-tone audiometry	69	62	70	not included
Perforated eardrum at examination	62	54	43	not included
Horizontal nystagmus at examination	35	-	14	not included
Doctor´s decision to treat, not necessarily with antibiotics but also with other medication	-	88	78	minor criterion (78)
Important improvement in symptoms reported by the patient or parent or in clinical findings in case further examination is possible, after a period of 14 days	-	72	70	not included

Items that reached ≥80% were automatically included in the definition. Items that achieved 60-79% agreement in Survey 2 were discussed again in Survey 3. Items that achieved 50-79% agreement in Survey 3 and newly suggested items by several members were discussed in Survey 4.

At Survey 4, members voted whether items should be considered as major or minor criterion or be included at all. We considered reaching consensus at ≥80% agreement for major criteria and ≥74% for minor criteria; items with <74% agreement were not included at all.

Table 4: Definitions of a sinonasal and an otologic exacerbation for children and adults with primary ciliary dyskinesia (PCD) participating in clinical research

I. Sinonasal exacerbation
All 3 of the following major criteria or 2 major and at least 2 minor criteria are needed to define a sinonasal exacerbation for children and adults with PCD in clinical research settings. **Major** criteria (included based on at least 80% consensus): • Patient-reported acute increase in nasal discharge or change in discharge colour • Patient-reported acute pain or sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead) • Mucopurulent nasal discharge at examination **Minor** criteria (included based on at least 74% consensus): • Patient-reported acute blocked nose or worsening in chronic feeling of blocked nose • Patient-reported acute decreased sense of smell • Increased mucus production or postnasal drip at examination • Signs of acute complication (e.g. orbital infection or abscess, meningitis, cerebral infection, cranial nerve palsy) at examination • Doctor´s decision to treat, not necessarily with antibiotics but also with increased upper airway clearance or other medication • Important improvement in symptoms reported by the patient or parent or in clinical findings in case further examination is possible, after a period of at least 14 days
II. Otologic exacerbation
3 of the following major criteria or 2 major and at least 2 minor criteria are needed to define an otologic exacerbation for children and adults with PCD in clinical research settings. **Majo**r criteria (included based on at least 80% consensus): • Patient-reported acute ear sensitivity or pain

- Patient-reported acute ear discharge
- Ear discharge at examination
- Signs of otitis media in otoscopy (i.e. erythema, collection)

Minor criteria (included based on at least 74% consensus):

- Patient-reported acute hearing problems/worsening in preexisting hearing problems
- Signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy) at examination
- Doctor´s decision to treat, not necessarily with antibiotics but also with other medication

These definitions are aimed to be used in research settings, especially in clinical trials, to define a sinonasal or otologic exacerbation in patients with PCD. No individual criterion is considered an absolutely requirement.

Definition of ENT exacerbations in PCD Consensus eDelphi Survey 1

Please read before completing the survey:

The aim of this project is to reach a consensus for defining exacerbations from the upper airways in people with PCD at the end of this eDelphi survey process.

This definition is meant to be used for clinical trials and other research and for clinical practice. At the first panel meeting, we concluded this standardised definition was missing and we decided unanimously to produce two separate definitions: one for sinonasal exacerbations (from the nose and sinuses) and one for otologic exacerbations (from the ears).

At the second panel meeting, we presented: 1) a summary of first opinions from the ENT experts about these definitions (anonymously) and 2) the results of the literature review we performed separately for nose/ sinuses (including the EPOS definition for non-PCD rhinosinusitis which was highlighted by several members) and ears. Based on both experts' first opinions and existing literature, we have identified the following 4 main points as important components for both definitions:

1) new symptoms/ worsening of baseline symptoms or quality of life
2) clinical signs/changes in clinical examinations
3) physician´s decision to treat/change management
4) complete resolution of changes/return to baseline

In this first eDelphi survey we include questions about these main components so we can reach a consensus which should be included in each definition. As the eDelphi surveys go on, we will go into more detail about the chosen components to decide e.g. which symptoms or which signs (if symptoms or signs are selected respectively).

Your replies will remain anonymous to the panel and only the moderating team will have access to your identifying information.

Please make sure you reply all questions.

I. Few questions about your background and your relationship to PCD

- Your name

(text box)

- Country you work/live in
  (text box)
- Are you (please select one of the following categories):
  ENT specialist
  Pulmonologist (paediatric or adult)
  Nurse
  Physiotherapist
  Epidemiologist
  Person with PCD or parent of child with PCD

- How many years do you have experience with PCD?

- If you are an ENT specialist do you manage?
  children with PCD
  adults with PCD
  both children and adults
  not an ENT specialist

- If you are ENT specialist, do you perform?
  ear surgery
  sinonasal surgery

II. Sinonasal exacerbation in people with PCD (linked to the nose and sinuses)

- What is your opinion about each of the following statements?

(choose of the following: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

Exacerbations from the nose and sinuses are an important problem for adults with PCD.

Exacerbations from the nose and sinuses are an important problem for children with PCD.

Exacerbations from the nose and sinuses impact the quality of life of people with PCD.

Exacerbations from the nose and sinuses always occur together with exacerbations from the ears in people with PCD.

Exacerbations from the nose and sinuses always occur together with exacerbations from the lungs in people with PCD.

Exacerbations from the nose and sinuses are not always dependent on upper airway disease baseline severity in people with PCD.

Exacerbations from the nose and sinuses can be an important outcome measure for ENT clinical trials in PCD.

- Do you have any other relevant comments on the importance of sinonasal exacerbations? (text box)

- In your opinion which of the following components can provide the best definition for an exacerbation from the nose and sinuses:
  (choose of the following: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

New symptoms/ worsening of baseline symptoms from the nose and sinuses, in isolation

Clinical signs/changes in clinical examinations of the nose and sinuses (e.g. nasal endoscopy), in isolation

Changes in imaging (CT or other) of the nose and sinuses in isolation

Decision of ENT specialist to treat, in isolation

Combination of symptoms and changes in clinical examination

Combination of symptoms and decision of ENT specialist to treat

Combination of symptoms and changes in imaging

Combination of changes in clinical examinations and decision of ENT specialist to treat

Combination of changes in clinical examinations and changes in imaging

Changes in imaging and decision of ENT specialist to treat

Combination of symptoms and changes in clinical examinations and decision of ENT specialist to treat

Combination of symptoms and changes in clinical examinations and imaging

Combination of symptoms and changes in imaging and decision of ENT specialist to treat

Combination of symptoms, changes in clinical examinations and imaging and decision of ENT specialist to treat

- What is your opinion about the following statement:
  (choose of the following: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

Complete resolution of any changes/return to baseline is an important element for the definition of exacerbations from the nose and sinuses in PCD

- Do you have anything to add regarding the general components for the definition of sinonasal exacerbations (remember, we will go into detail in the next surveys) or do you have any comment explaining your replies?
  (text box)

III. Otologic exacerbation in people with PCD (linked to the ears)

- What is your opinion about each of the following statements?
  (choose of the following: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

Exacerbations from the ears are an important problem for adults with PCD.

Exacerbations from the ears are an important problem for children with PCD.

Exacerbations from the ears impact the quality of life of people with PCD.

Exacerbations from the ears always occur together with exacerbations from the nose and sinuses in people with PCD.

Exacerbations from the ears always occur together with exacerbations from the lungs in people with PCD.

Exacerbations from the ears are not always dependent on upper airway disease baseline severity in people with PCD.

Exacerbations from the ears can be an important outcome measure for ENT clinical trials in PCD.

- Do you have any other relevant comments on the importance of otologic exacerbations?
  (text box)

- In your opinion which of the following components can provide the best definition for an exacerbation from the ears:
  (choose of the following: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

New symptoms/ worsening of baseline symptoms from the ears, in isolation

Clinical signs/changes in clinical examinations of the ears (e.g. otoscopy, audiometry), in isolation

Decision of ENT specialist to treat, in isolation

Combination of symptoms and changes in clinical examinations

Combination of symptoms and decision of ENT specialist to treat

Combination of changes in clinical examinations and decision of ENT specialist to treat

Combination of symptoms and changes in clinical examinations and decision of ENT specialist to treat

- What is your opinion about the following statement:
  (choose of the following: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

Complete resolution of any changes/return to baseline is an important element for the definition of exacerbations from the ears in PCD.

- Do you have anything to add regarding the general components for the definition of otologic exacerbations (remember, we will go into detail in the next surveys) or do you have any comment explaining your replies?
  (text box)

  Thank you for completing this survey, please contact myrofora.goutaki@unibe.ch if you have any questions.

Definition of ENT exacerbations in PCD Consensus eDelphi Survey 2

Please read before completing the survey:

We would like to remind you that the aim of this project is to reach a consensus for defining exacerbations from the upper airways in people with PCD at the end of this eDelphi survey process.

This definition is meant to be used for clinical trials and other research and for clinical practice. We decided unanimously to produce two separate definitions: one for sinonasal exacerbations and one for otologic exacerbations.

With the first survey, we assessed opinions about the importance of sinonasal and otologic exacerbations for people with PCD and about the components that should be included in the exacerbation definitions. We achieved 100% participation of panel and patient advisory group members in the first survey.

After evaluating all responses and comments, we have now developed this second survey that includes questions to help us get closer to a consensus for the definition of sinonasal and otologic exacerbations. This second survey is longer as it is going into more details about the components highlighted in the first survey and will help decide on all included elements. A next survey based on these results will help to clarify open questions.

Your replies will remain anonymous to the panel and only the moderating team will have access to your identifying information.

IV. Few questions about your background and your relationship to PCD

- Name
  (text box)
- Country you work/live in
  (text box)

V. Sinonasal exacerbation in people with PCD (linked to the nose and sinuses)

In the first survey, we reached consensus (more than 80% agreed or strongly agreed) on the following statements about the importance of sinonasal exacerbations:

1. Exacerbations from the nose and sinuses are an important problem for adults with PCD.
2. Exacerbations from the nose and sinuses are an important problem for children with PCD.
3. Exacerbations from the nose and sinuses impact the quality of life of people with PCD.
4. Exacerbations from the nose and sinuses can be an important outcome measure for ENT clinical trials in PCD.

We also reached consensus about sinonasal exacerbations occurring also separately from pulmonary or otologic exacerbations.

- Do you have any additional comments about the importance of sinonasal exacerbations?
  (text box)

In the first survey, the respondents said that the combination of new symptoms/ worsening of baseline symptoms and of clinical signs/ changes in clinical examination is the best combination of components to define sinonasal exacerbations.

<u>Change in symptoms</u>

- Should changes in the following symptoms be included as an indication of a sinonasal exacerbation?

(5 level system: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

Fever/Temperature above 38°C

Blocked nose

Increase in nasal discharge or change in discharge colour

Decreased sense of smell

Pain/sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead)

Headache

Malaise, fatigue, tiredness

Increased cough

Sore throat

Bad breath

Bad sleep

Reduced quality of life (QoL) evaluated by any sinonasal specific QoL questionnaire

- Are there any other symptoms, which should be included as an indication of a sinonasal exacerbation? Please explain (text box)
- Please rank the 3 most important symptoms (from the list above or any additional) for inclusion in the definition

Changes in clinical examinations

- Should the following clinical signs/changes in examinations be included as an indication of a sinonasal exacerbation? (Note: this would mean that the agreed upon examinations should be performed in all people with PCD to diagnose a sinonasal exacerbation) (yes or no)

Erythema or oedema of nasal mucosa

Mucopurulent nasal discharge

Increased mucus production or postnasal drip

Swelling of inferior turbinates

Appearance or swelling of nasal polyps

Positive microbiology culture from nasal or sinus discharge

Reduced sense of smell measured by any olfactory test (smell test)

Signs of acute complication (e.g. orbital infection/abscess, meningitis, cerebral infection, cranial nerve palsy)

Negative allergy tests (to exclude allergic causes)

Blood tests for indications of infection (e.g. neutrophils)

- Are there any other findings of clinical examinations, which should be included as an indication of a sinonasal exacerbation? Please explain (text box)
- Please rank the 3 most important examination findings (from the list above or any additional) for inclusion in the definition

In the first round of the survey, there was no consensus that changes in imaging should be a requirement for the definition of a sinonasal exacerbation. However, a majority indicated that it might contribute in combination with changes in symptoms and clinical examinations.

- Should a change in sinus imaging be an absolute requirement for the definition of a sinonasal exacerbation and therefore should it be performed in all people with PCD to diagnose a sinonasal exacerbation?
  (2 choices: Agree, Disagree)
- Please explain your vote above (text box)

In the first round of the survey, there was no consensus that decision of ENT specialist to treat should be a requirement for the definition of a sinonasal exacerbation. However, a majority indicated that it might contribute in combination with changes in symptoms and clinical examinations.

- Should the decision of ENT specialist to treat be an absolute requirement for the definition of a sinonasal exacerbation?
  (2 choices: Agree, Disagree)
- Please explain your vote above (text box)
- If the decision of an ENT specialist to treat is considered for the definition, which of the following treatments should be considered (one choice only possible):
  Prescription of antibiotics
  Changes in non-antibiotic management (e.g. upper airways clearance or other medication)
  Any of the two
  None, it should not be part of the definition

In the first round of the survey, there was no consensus that complete resolution of any changes/return to baseline should be a component for the definition of sinonasal exacerbation. A majority indicated that it might be important to include. Others stated that complete resolution is not possible in many cases so it cannot be an absolute requirement for the definition.

- Should complete resolution and return to baseline be an absolute requirement for the definition of a sinonasal exacerbation?
  (2 choices: Agree, Disagree)
- Should an important improvement in symptoms/clinical findings after a period of time be an absolute requirement for the definition of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

- Please explain your votes above (text box)

- Do you have any further comments about the definition of sinonasal exacerbations? (text box)

VI. Otologic exacerbation in people with PCD (linked to the ears)

In the first survey, we reached consensus (more than 80% agreed or strongly agreed) on the following statements about the importance of otologic exacerbations:

1. Exacerbations from the ears are an important problem for children with PCD.
2. Exacerbations from the ears impact the quality of life of people with PCD.
3. Exacerbations from the ears can be an important outcome measure for ENT clinical trials in PCD.

Respondents did not reach a consensus that otologic exacerbations are an important problem for adults with PCD but a majority voted that it is.

- In your opinion, are exacerbations from the ears an important problem for adults with PCD? (2 choices: Agree, Disagree)
- Please explain your vote above, especially if you disagree with the statement (text box)

We also reached consensus about otologic exacerbations occurring also separately from pulmonary or sinonasal exacerbations.

- Do you have any additional comments about the importance of otologic exacerbations? (text box)

In the first survey, the respondents said that the combination of new symptoms/ worsening of baseline symptoms and of clinical signs/ changes in clinical examination is the best combination of components to define otologic exacerbations. Decision of an ENT specialist to treat in addition to this combination, was the second most popular choice (also reached consensus).

<u>Change in symptoms</u>

- Should changes in the following symptoms be included as an indication of an otologic exacerbation?

(5 level system: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

Fever/Temperature above 38°C

Ear/sensitivity pain

Ear discharge

Tinnitus or ringing in the ears

A feeling of fullness in the ears

Hearing problems

Difficulty for communication

Malaise, fatigue, tiredness

Headache

Dizziness, vertigo

- Are there any other symptoms, which should be included as an indication of an otologic exacerbation? Please explain (text box)
- Please rank the 3 most important symptoms (from the list above or any additional) for inclusion in the definition

Changes in clinical examinations

- Should the following clinical signs/changes in examinations be included as an indication of an otologic exacerbation? (yes or no)

Perforated eardrum

Ear discharge

Nystagmus

Signs of otitis media in otoscopy (i.e. erythema, collection)

Pathologic tympanometry findings

Signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy…)

Impaired hearing tested by pure-tone audiometry (air and bone-conduction)

Positive microbiology culture from ear discharge

Blood tests for indications of infection (e.g. neutrophils)

- Are there any other findings of clinical examinations, which should be included as an indication of an otologic exacerbation? Please explain (text box)
- Please rank the 3 most important examination findings (from the list above or any additional) for inclusion in the definition

Decision of ENT specialist to treat

- Should the decision of ENT specialist to treat be an absolute requirement for the definition of an otologic exacerbation?

(5 level system: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree)

- If the decision of an ENT specialist to treat is considered for the definition, which of the following treatments should be considered (one choice only possible):

Prescription of antibiotics (either local or systemic)
Changes in non-antibiotic management (e.g. ear antiseptic or other medication)
Any of the two
None, it should not be part of the definition

In the first round of the survey, there was no consensus that complete resolution of any changes/return to baseline should be a component for the definition of otologic exacerbation. A majority indicated that it might be important to include. Others stated that complete resolution is not possible in many cases so it cannot be an absolute requirement for the definition.

- Should complete resolution and return to baseline be an absolute requirement for the definition of an otologic exacerbation?
  (2 choices: Agree, Disagree)
- Should an important improvement in symptoms/clinical findings after a period of time be an absolute requirement for the definition of an otologic exacerbation?
  (2 choices: Agree, Disagree)
- Please explain your votes above (text box)

- Do you have any further comments about the definition of otologic exacerbations? (text box)

Thank you for completing this survey, please contact myrofora.goutaki@unibe.ch if you have any questions.

Definition of ENT exacerbations in PCD Consensus eDelphi Survey 3

Please read before completing the survey:

We would like to remind you that the aim of this project is to reach a consensus for defining exacerbations from the upper airways in people with PCD at the end of this eDelphi survey process.

This definition is meant to be used for clinical trials and other research and for clinical practice.

With the first survey, we assessed opinions about the importance of sinonasal and otologic exacerbations for people with PCD and about the components that should be included in the exacerbation definitions and with the second we went into the specific elements for the relevant components where we reached consensus. We achieved 100% participation of the panel and a very good participation from the patient advisory group members in both surveys.

After evaluating all responses and comments, we have now developed this third survey that clarifies opinions on the elements that were voted on in the previous one and aims to finalise all components and elements for the two definitions. This third survey is also long but allow us to decide on all the elements included in the two definitions.

A next last survey based on these results will help to clarify all remaining open questions. We aim to organise a group meeting after analysing the 3rd survey results and before drafting the 4th survey to make sure we discuss all important points that needs to be included in survey 4.

Your replies will remain anonymous to the panel and only the moderating team will have access to your identifying information.

VII. Few questions about your background and your relationship to PCD

- Name
  (text box)
- Country you work/live in
  (text box)

VIII. Sinonasal exacerbation in people with PCD (linked to the nose and sinuses)

<u>Change in symptoms</u>

In the second survey, we reached consensus (more than 80% agreed or strongly agreed) that the following 3 symptoms (or worsening in them) should be included as an indication of a sinonasal exacerbation. These 3 symptoms were also ranked as the 3 most important by the majority of participants with great difference in votes from all others.

- Increase in nasal discharge or change in discharge colour
- Pain/sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead)
- Blocked nose

1. What is your opinion about the inclusion of changes in clinical symptoms in the definition (choose one):

- A patient should have ALL symptoms that we will include in the definition to be considered as having a sinonasal exacerbation.
- We should include a list of relevant important symptoms of which a patient should have a combination but NOT ALL, to be considered as having a sinonasal exacerbation.

In the second round of the survey, there was <u>no consensus</u> about the inclusion of the following symptoms in the definition as an indication of a sinonasal exacerbation. However, they were voted as important by 55-75% of participants and were ranked among the 3 most important symptoms by few.

2. Should reduced quality of life evaluated by any sinonasal specific quality of life (QoL) questionnaire be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

3. Please explain your vote above (text box)
4. Should decreased sense of smell be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

5. Please explain your vote above (text box)
6. Should headaches be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

7. Please explain your vote above (text box)
8. Should bad sleep be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

9. Please explain your vote above (text box)
10. Should cough be included in the definition as an indication of a sinonasal exacerbation?

(3 choices: Agree for all, Agree only for children, Disagree)

11. Please explain your vote above (text box)

12. Are there any other symptoms not mentioned so far in this survey, which you find very important for a sinonasal exacerbation and you would like to discuss/put up for voting again?

(Text box)

Changes in clinical examinations

In the second survey, we reached consensus (more than 80% agreed or strongly agreed) that the following 2 clinical signs/changes in examinations be included as an indication of a sinonasal exacerbation. These 2 clinical signs/changes in examinations were also ranked as the 2 most important by the majority of participants with great difference in votes from all others.

- Mucopurulent nasal discharge
- Increased mucus production or postnasal drip

13. What is your opinion about the inclusion of clinical signs/changes in examinations in the definition (choose one):

- A patient should have ALL clinical signs/changes in examinations that we will include in the definition to be considered as having a sinonasal exacerbation.
- We should include a list of relevant important clinical signs/changes in examinations of which a patient should have a combination but NOT ALL, to be considered as having a sinonasal exacerbation.

In the second round of the survey, there was no consensus about the inclusion of the following clinical signs/changes in examinations in the definition as an indication of a sinonasal exacerbation. However, they were voted as important by 55-75% of participants and were ranked among the 3 most important clinical signs/changes in examinations by few.

14. Should signs of acute complication (e.g. orbital infection/abscess, meningitis, cerebral infection, cranial nerve palsy) be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

15. Please explain your vote above (text box)
16. Should appearance or swelling of nasal polyps be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

17. Please explain your vote above (text box)
18. Should erythema or oedema of nasal mucosa be included in the definition as an indication of a sinonasal exacerbation?

(2 choices: Agree, Disagree)

19. Please explain your vote above (text box)

20. Are there any other clinical signs/changes in examinations not mentioned so far in this survey, which you find very important for a sinonasal exacerbation and you would like to discuss/put up for voting again?
    (Text box)

In the second round of the survey, we reached consensus (more than 80% agreed or strongly agreed) that changes in imaging should not be a requirement for the definition of a sinonasal exacerbation.

<u>Decision to treat and resolution of changes</u>

In the second round of the survey, there was no consensus about including or not including decision of ENT specialist to treat as a requirement for the definition of a sinonasal exacerbation. However, a majority indicated that it might contribute in combination with changes in symptoms and clinical examinations.

21. What is your opinion on the following statements related to sinonasal exacerbations
    (2 choices for all: Agree, Disagree)

- Decision to treat might be subjective and should not be included especially for the use of the definition in clinical trials.
- Decision to treat is based on the changes of symptoms and clinical examinations and does not need to be included in the definition in addition to those.
- Decision to treat is more relevant for the use of the definition in clinical practice, however we should include other physicians e.g. paediatrician, general practitioner as in reality, not all patients need to visit an ENT to diagnose a sinonasal exacerbation.
- Decision to treat not necessarily with antibiotics but also with increased upper airways clearance or other medication, could be included in the definition as a less important point (e.g. possibly a minor criterion).

22. Do you have any comments about these statements?
    (text box)

In the second round of the survey, we reached consensus that complete resolution of any changes and return to baseline should not an absolute requirement for the definition of sinonasal exacerbation. However, a majority of participants voted that an important improvement in symptoms/clinical findings after a period of time should be an absolute requirement for the definition of a sinonasal exacerbation.

23. What is your opinion on the following statements:

- An important improvement in symptoms/clinical findings after a period of time should be included in the definition of a sinonasal exacerbation as a less important point (e.g. possibly a minor criterion).
- The absence of improvement in symptoms/clinical findings does not eliminate the diagnosis of acute sinonasal exacerbation.

(2 choices: Agree, Disagree)

24. Please explain your vote above (text box)

25. Do you have any further comments about the definition of sinonasal exacerbations? (text box)

IX. Otologic exacerbation in people with PCD (linked to the ears)

In the second survey, we did not reach a consensus that otologic exacerbations are an important problem for adults, however many participants commented that they only disagreed because otologic exacerbations are less common in adults.

26. What is your opinion on the following statement:

- Exacerbations from the ears are less common than chronic problems in adults with PCD, however when they occur, they can be an important problem.
  (2 choices: Agree, Disagree)

27. Please explain your vote above (text box)

<u>Change in symptoms</u>

In the second survey, we reached consensus (more than 80% agreed or strongly agreed) that the following 3 symptoms (or worsening in them) should be included as an indication of an otologic exacerbation. These 3 symptoms were also ranked as the 3 most important by the majority of participants with great difference in votes from all others.

- Ear sensitivity/pain
- Ear discharge
- Hearing problems

28. What is your opinion about the inclusion of changes in clinical symptoms in the definition (choose one):

- A patient should have ALL symptoms that we will include in the definition to be considered as having an otologic exacerbation.
- We should include a list of relevant important symptoms of which a patient should have a combination but NOT ALL, to be considered as having an otologic exacerbation.

In the second round of the survey, there was no consensus about the inclusion of the following symptom in the definition as an indication of an otologic exacerbation. However, it was voted as important by 77% of participants and was ranked among the 3 most important symptoms by many.

29. Should a feeling of fullness in the ears be included in the definition as an indication of an otologic exacerbation?

(2 choices: Agree, Disagree)

30. Please explain your vote above (text box)
31. Are there any other symptoms not mentioned so far in this survey, which you find very important for an otologic exacerbation and you would like to discuss/put up for voting again?

(Text box)

Changes in clinical examinations

In the second survey, we reached consensus (more than 80% agreed or strongly agreed) that the following two clinical signs/changes in examinations be included as an indication of an otologic exacerbation. These 2 clinical signs/changes in examinations were also ranked as the 2 most important by the majority of participants with great difference in votes from all others.

- Ear discharge
- Signs of otitis media in otoscopy (i.e. erythema, collection)

32. What is your opinion about the inclusion of clinical signs/changes in examinations in the definition (choose one?):

- A patient should have ALL clinical signs/changes in examinations that we will include in the definition to be considered as having an otologic exacerbation.
- We should include a list of relevant important clinical signs/changes in examinations of which a patient should have a combination but NOT ALL, to be considered as having an otologic exacerbation.

In the second round of the survey, there was no consensus about the inclusion of the following clinical signs/changes in examinations in the definition as an indication of an otologic exacerbation. However, they were voted as important by 50-75% of participants and were ranked among the 3most important clinical signs/changes in examinations by few.

33. Should signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy) be included in the definition as an indication of an otologic exacerbation?
    (2 choices: Agree, Disagree)
34. Please explain your vote above (text box)
35. Should impaired hearing tested by pure-tone audiometry be included in the definition as an indication of an otologic exacerbation?
    (2 choices: Agree, Disagree)
36. Please explain your vote above (text box)
37. Should a perforated eardrum be included in the definition as an indication of an otologic exacerbation?
    (2 choices: Agree, Disagree)
38. Please explain your vote above (text box)
39. Should pathologic tympanometry be included in the definition as an indication of an otologic exacerbation?
    (2 choices: Agree, Disagree)
40. Please explain your vote above (text box)
41. Should pathologic pneumatic otoscopy be included in the definition as an indication of an otologic exacerbation, particularly when tympanometry is not available?
    (2 choices: Agree, Disagree)
42. Please explain your vote above (text box)

43. Are there any other clinical signs/changes in examinations not mentioned so far in this survey, which you find very important for an otologic exacerbation and you would like to discuss/put up for voting again?
    (Text box)

Decision to treat and resolution of changes

In the second round of the survey, there was no consensus about including or not including decision of ENT specialist to treat as a requirement for the definition of an otologic exacerbation. However, a majority indicated that it might contribute in combination with changes in symptoms and clinical examinations.

44. What is your opinion on the following statements related to otologic exacerbations?
    (2 choices for all: Agree, Disagree)

- Decision to treat might be subjective and should not be included especially for the use of the definition in clinical trials.
- Decision to treat is based on the changes of symptoms and clinical examinations and does not need to be included in the definition in addition to those.
- Decision to treat is more relevant for the use of the definition in clinical practice, however we should include other physicians e.g. paediatrician, general practitioner as in reality, not all patients need to visit an ENT to diagnose an otologic exacerbation.
- Decision to treat not necessarily with antibiotics but also with other medication, could be included in the definition as a less important point (e.g. possibly a minor criterion).
-

45. Do you have any comments about these statements?
    (text box)

In the second round of the survey, we reached consensus that complete resolution of any changes and return to baseline should not an absolute requirement for the definition of otologic exacerbation. However, a majority of participants voted that an important improvement in symptoms/clinical findings after a period of time should be an absolute requirement for the definition of an otologic exacerbation.

46. What is your opinion on the following statements:

- An important improvement in symptoms/clinical findings after a period of time should be included in the definition as a less important point (e.g. possibly a minor criterion), as it is not always possible (e.g. in case of a perforated eardrum)
- The absence of improvement in symptoms/clinical findings does not eliminate the diagnosis of acute otologic exacerbation.

(2 choices: Agree, Disagree)

47. Please explain your vote above (text box)
48. Do you have any further comments about the definition of otologic exacerbations? (text box)

X. These last questions relates to BOTH definitions (sinonasal and otologic):

49. Do you agree with the idea of introducing major and minor criteria to the definition (to decide which belong to major or minor category in the last survey)?

(2 choices: Agree, Disagree)

In the second round of the survey, several participants highlighted the need to assess all clinical examinations findings in comparison to previous (baseline) evaluations.

50. Should we include the following statement as comment to our definitions related to clinical signs and changes in examinations?

All clinical signs/changes to clinical examinations should be assessed in relation to previous examinations.

(2 choices: Agree, Disagree)

51. Please explain your vote above (text box)

Thank you for completing this survey and for participating to this project, please contact myrofora.goutaki@unibe.ch if you have any questions.

Definition of ENT exacerbations in PCD Consensus eDelphi Survey 4

Please read carefully before completing the survey:

This is the 4th and final survey.

We would like to remind you that the aim of this project is to reach a consensus for defining exacerbations of the upper airways in people with PCD at the end of this eDelphi survey process.

With the previous surveys, we assessed opinions about the importance of sinonasal and otologic exacerbations for people with PCD. We selected the components that should be included in the exacerbation definitions as well as the specific elements for the relevant components where we reached consensus.

In the third survey, 100% of participants agreed to introduce major and minor criteria to the definitions. In this fourth and last survey, we will decide which specific elements will be considered as major and which as minor for each definition and will clarify any remaining important points.

Your replies will remain anonymous to the panel and only the moderating team will have access to your identifying information.

XI. Few questions about your background and your relationship to PCD

- Name
  (text box)
- Country you work/live in
  (text box)

XII. Sinonasal exacerbation in people with PCD (linked to the nose and sinuses)

Change in symptoms: In the previous surveys, we reached consensus (96% agreed) that **the definition should include a list of relevant important symptoms of which a patient should have a combination** but NOT ALL, to be considered as having a sinonasal exacerbation. We also reached consensus (more than 80% agreed or strongly agreed) that the following 3 symptoms (or worsening in them) should be included as an indication of a sinonasal exacerbation: **i) increase in nasal discharge or change in discharge colour, ii) pain/sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead) or iii) blocked nose.**

Changes in clinical examinations: In the previous surveys, we reached consensus (96% agreed) **that the definition should include a list of relevant important clinical signs/changes in examinations of which a patient should have a combination** but NOT ALL, to be considered as having a sinonasal exacerbation. We also reached consensus (more than 80% agreed or strongly agreed) that the following 2 clinical signs/changes in examinations should be included as an indication of a sinonasal exacerbation**: i) mucopurulent nasal discharge or ii) increased mucus production or postnasal drip.**

Decision to treat and resolution of changes: In the last survey we reached consensus (more than 80% agreed) that **decision to treat not necessarily with antibiotics but also with increased upper airway clearance or other medication, could be included in the definition as a less important point** (e.g. possibly a minor criterion). Regarding the resolution of changes, we reached consensus **that an important improvement in symptoms/clinical findings after a period of time should be included in the definition of a sinonasal exacerbation as a less important point** (e.g. possibly a minor criterion). We also reached consensus that **absence of improvement in symptoms/clinical findings does not eliminate the diagnosis of acute sinonasal exacerbation**

and we will add this as a clarification to the definition. Based on some comments, the wording was not clear enough to be useful in a clinical trial and the period of time should be further defined.

1. Using the major and minor criteria approach, we will include some criteria which are most important for the definition (major) and some which are less important (minor). A combination of major or minor criteria is needed to reach the definition of sinonasal exacerbation.
Our suggestion is to include all criteria where we already reached a consensus as major unless we already reached consensus to include them as minor. Please state if you agree using the following criteria as major or minor. (Agree, include as major/ Disagree, include as minor)

- Reported increase in nasal discharge or change in discharge colour (Agree, include as major/ Disagree, include as minor)
- Reported pain/sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead) (Agree, include as major/ Disagree, include as minor)
- Reported blocked nose (Agree, include as major/ Disagree, include as minor)
- Mucopurulent nasal discharge at examination (Agree, include as major/ Disagree, include as minor)
- Increased mucus production or postnasal drip at examination (Agree, include as major/ Disagree, include as minor)
- Decision to treat, not necessarily with antibiotics but also with increased upper airway clearance or other medication (Agree, include as minor/ Disagree, do not include)
- Important improvement in symptoms reported by the patient or parent or in clinical findings in case further examination is possible, after a period of 14 days (Agree, include as minor/ Disagree, do not include)

2. Would you like to include any of the following criteria (symptoms or signs/changes in examination), which reached more than 50% but less than 80% consensus or were suggested to discuss again, as minor criteria in the definition?
Please state from the list below which you think should be minor criterion and which should not be included (Agree, include as minor/ Disagree, do not include)

- Reduced quality of life evaluated by any sinonasal specific quality of life questionnaire
- Reported decreased sense of smell
- Signs of acute complication (e.g. orbital infection/abscess, meningitis, cerebral infection, cranial nerve palsy) at examination
- Acute frontonasal / maxillary tenderness at examination

3. We previously listed 5 potential major criteria and 6 potential minor. **Our suggestion is that the definition for sinonasal exacerbation should include a) 3 major or b) 2 major and at least 2 minor criteria.**
Do you agree? Yes/ No
4. If you do not agree, please explain your opinion and make an alternative suggestion (text)
5. Do you have any further comments for the sinonasal definition? (text)

XIII. Otologic exacerbation in people with PCD (linked to the ears)

In the third survey, we reached consensus (95% agreed) that exacerbations from the ears are less common than chronic problems in adults with PCD, however when they occur, they can be an important problem.

Change in symptoms: In the previous surveys, we reached consensus (100% agreed) that **the definition should include a list of relevant important symptoms of which a patient should have a combination** but NOT ALL, to be considered as having an otologic exacerbation. We also reached consensus (more than 80% agreed or strongly agreed) that the following 3 symptoms (or worsening in them) should be included as an indication of an otologic exacerbation: i) **ear sensitivity/pain, ii) ear discharge or iii) hearing problems.**

Changes in clinical examinations: In the previous surveys, we reached consensus (92% agreed) that **the definition should include a list of relevant important clinical signs/changes in examinations of which a patient should have a combination** but NOT ALL, to be considered as having an otologic exacerbation. We also reached consensus (more than 80% agreed or strongly agreed) that the following 2 clinical signs/changes in examinations be included as an indication of an otologic exacerbation: i) **ear discharge or ii) signs of otitis media in otoscopy** (i.e. erythema, collection).

Decision to treat and resolution of changes: In the last survey we reached consensus (more than 80% agreed) that decision to treat not necessarily with antibiotics but also with other medication, could be included in the definition as a less important point (e.g. possibly a minor criterion). Regarding the resolution of changes, **we did not reach consensus that an important improvement in symptoms/clinical findings after a period of time should be included in the definition** as a less important point (e.g. possibly a minor criterion), **as it is not always possible** (e.g. in case of a perforated eardrum). However 77% of participants agreed with the sentence above. **We reached consensus that absence of improvement in symptoms/clinical findings does not eliminate the diagnosis of acute otologic exacerbation** and we will add this as a clarification to the definition. Based on some comments, the wording was not clear enough to be useful in a clinical trial and the period of time should be further defined.

6. Using the major and minor criteria approach, we will include some criteria which are most important for the definition (major) and some which are less important (minor). A combination of major or minor criteria is needed to reach the definition of otologic exacerbation.

Our suggestion is to include all criteria where we already reached a consensus as major unless we already reached consensus to include them as minor. Please state if you agree using the following criteria as major or minor (Agree, include as major/ Disagree, include as minor)

- Reported ear sensitivity/pain (Agree, include as major/ Disagree, include as minor)
- Reported ear discharge (Agree, include as major/ Disagree, include as minor)
- Reported hearing problems (Agree, include as major/ Disagree, include as minor)
- Ear discharge at examination (Agree, include as major/ Disagree, include as minor)
- Signs of otitis media in otoscopy (i.e. erythema, collection) (Agree, include as major/ Disagree, include as minor)
- Decision to treat, not necessarily with antibiotics but also with other medication (Agree, include as minor/ Disagree, do not include)

7. Would you like to include any of the following criteria, which reached more than 50% but less than 80% consensus or were suggested to discuss again, as minor criteria in the definition? Please state from the list below which you think should be minor criterion and which should not be included. (Agree, include as minor/ Disagree, do not include)
   - Reported feeling of fullness in the ears
   - Signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy) at examination
   - Impaired hearing tested by pure-tone audiometry
   - Perforated eardrum at examination
   - Horizontal nystagmus at examination
   - Important improvement in symptoms reported by the patient or parent or in clinical findings in case further examination is possible, after a period of 14 days

8. We previously listed 5 potential major criteria and 7 potential minor. **Our suggestion is that the definition for otologic exacerbation should include a) 3 major or b) 2 major and at least 2 minor criteria.**
Do you agree? Yes/ No
9. If you do not agree, please explain your opinion and make an alternative suggestion (text)
10. Do you have any further comments for the otologic definition? (text)

XIV. These last points relate to BOTH definitions (sinonasal and otologic):

In the last round of the survey we reached consensus (85% agreed) that all clinical signs/changes to clinical examinations should be assessed in relation to previous examinations. This was highlighted as particularly important for research settings and will be added as a clarification to the definitions.

11. We also received comments highlighting that realistically clinical practice may differ substantially than research practices, especially for patients residing far from the ENT specialist who follows them for PCD. For this reason, we suggest to include the following clarification for both definitions:
"These definitions are aimed to be used in research settings, especially in clinical trials, to define a sinonasal or otologic exacerbation in patients with PCD".

We will also add a section in the manuscript discussion, explaining that the definitions could also be useful in clinical practice, discussing specific points that might differ, such as a different number of major or minor criteria.
Do you agree? Yes/ No

12. If you do not agree, please explain and suggest a different wording (text)
13. Would you like us to organise a zoom call to discuss further the final definitions? Yes/No
14. Is there anything else you would like to add in this last survey? (text)

Thank you for completing this survey and for participating in this project! Please contact myrofora.goutaki@unibe.ch if you have any questions.

Table S1: Composition of the consensus panel and the patient volunteer group and participation to the electronic Delphi surveys

Members of consensus panel (N=24)		Responded to Survey 1 (N=24)	Responded to Survey 2 (N=23)	Responded to Survey 3 (N=23)	Responded to Survey 4 (N=21)
ENT specialist	17	17	16	16	15
Paediatric pulmonologist	1	1	1	1	0
Adult pulmonologist	1	1	1	1	1
Physiotherapist	2	2	2	2	2
Clinical epidemiologist	1	1	1	1	1
Nurse specialist	1	1	1	1	1
Patient representatives	2	2	2	2	2
		100%	96%	96%	88%
Patient volunteers	-	5	3	3	2

ENT: Ear-Nose-Throat

Patient volunteers were not members of the consensus panel; they were encouraged to participate to the surveys but there was no required minimum number to proceed to the next survey.

Table S2: Responses to key questions of eDelphi survey 1

	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Mean	% of agreement
1) Sinonasal exacerbation definition							
Which of the following components can provide the best definition for an exacerbation from the nose and sinuses:							
New symptoms or worsening of baseline symptoms from the nose and sinuses, in isolation	2	3	7	10	7	3.59	59
Clinical signs or changes in clinical examinations of the nose and sinuses (e.g. nasal endoscopy), in isolation	3	6	7	9	5	3.34	48
Changes in imaging (CT or other) of the nose and sinuses in isolation	5	5	9	7	3	2.93	34
Decision of ENT specialist to treat, in isolation	3	7	11	6	1	2.72	24
Combination of symptoms and changes in clinical examination	0	0	2	14	13	4.66	93
Combination of symptoms and decision of ENT specialist to treat	1	1	10	11	7	3.86	62
Combination of symptoms and changes in imaging	3	2	5	15	4	3.52	66
Combination of changes in clinical examinations and decision of ENT specialist to treat	1	1	14	8	5	3.24	45
Combination of changes in clinical examinations and changes in imaging	2	3	10	11	3	3.45	48
Changes in imaging and decision of ENT specialist to treat	2	7	12	5	3	3.00	28
Combination of symptoms and changes in clinical examinations and decision of ENT specialist to treat	0	1	6	5	17	4.31	76
Combination of symptoms and changes in clinical examinations and imaging	2	1	5	12	9	3.86	72
Combination of symptoms and changes in imaging and decision of ENT specialist to treat	2	2	10	10	5	3.48	52

Combination of symptoms, changes in clinical examinations and imaging and decision of ENT specialist to treat	2	2	6	5	14	3.93	66
Complete resolution of any changes or return to baseline is an important element for the definition of exacerbations from the nose and sinuses in PCD	0	2	7	13	7	3.8 6	69
2) Otologic exacerbation definition							
Which of the following components can provide the best definition for an exacerbation from the ears:							
New symptoms or worsening of baseline symptoms from the ears, in isolation	1	2	8	12	5	3.52	59
Clinical signs or changes in clinical examinations of the ears (e.g. otoscopy, audiometry), in isolation	1	5	6	12	5	3.64	59
Decision of ENT specialist to treat, in isolation	3	7	12	4	3	3.17	24
Combination of symptoms and changes in clinical examination	0	0	1	16	12	4.38	97
Combination of symptoms and decision of ENT specialist to treat	1	1	10	11	6	3.69	62
Combination of changes in clinical examinations and decision of ENT specialist to treat	1	1	13	9	5	3.55	48
Combination of symptoms and changes in clinical examinations and decision of ENT specialist to treat	1	1	3	9	16	4.41	86
Complete resolution of any changes or return to baseline is an important element for the definition of exacerbations from the ears in PCD	1	2	4	19	3	3.72	76

ENT: Ear-Nose-Throat, CT: computed tomography, PCD: primary ciliary dyskinesia

Table S3: Responses to key questions of eDelphi survey 2 regarding clinical symptoms

	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Mean	% of agreement
1) Should changes in the following symptoms be included as an indication of a sinonasal exacerbation?							
Fever/Temperature above 38°C	2	6	11	4	3	3.31	27
Blocked nose	0	1	1	14	10	4.27	92
Increase in nasal discharge or change in discharge colour	0	0	0	8	18	4.69	100
Decreased sense of smell	0	2	6	12	6	3.85	69
Pain or sensitivity in the sinus region (i.e. around the nose, eyes, on the cheeks or forehead)	0	2	2	8	14	4.31	85
Headache	0	2	9	13	2	3.58	58
Malaise/fatigue	1	6	9	6	4	3.23	38
Increased cough	0	6	6	11	3	3.42	54
Sore throat	5	6	9	3	1	2.54	15
Bad breath	1	8	8	6	2	3.00	31
Bad sleep	2	5	5	13	1	3.23	54
Reduced QoL evaluated by any sinonasal specific QoL questionnaire	1	0	6	10	9	4.00	73
2) Should changes in the following symptoms be included as an indication of an otologic exacerbation?							
Fever/Temperature above 38°C	3	3	10	8	2	3.12	38
Ear sensitivity or pain	0	1	1	13	11	4.31	92
Ear discharge	0	1	1	9	15	4.46	92
Tinnitus or ringing in the ears	1	4	12	9	0	3.12	35
A feeling of fullness in the ears	1	2	3	15	5	3.81	77

Hearing problems	1	0	3	14	8	4.08	85
Difficulty in communication	0	5	12	6	3	3.27	35
Malaise/fatigue	2	6	12	5	1	2.88	23
Headache	2	7	10	5	2	2.92	27
Dizziness/vertigo	0	3	12	8	3	3.42	42

QoL: quality of life. Symptoms in red were ranked as the most important in their category.

Table S4: Responses to key questions of eDelphi survey 2 regarding clinical signs and examinations

	% of agreement
1) Should the following clinical signs/changes in examinations be included as an indication of a sinonasal exacerbation?	
Erythema or oedema of nasal mucosa	54
Mucopurulent nasal discharge	100
Increased mucus production or postnasal drip	92
Swelling of inferior turbinates	42
Appearance or swelling of nasal polyps	58
Positive microbiology culture from nasal or sinus discharge	35
Reduced sense of smell measured by any olfactory test	27
Signs of acute complication (e.g. orbital infection or abscess, meningitis, cerebral infection, cranial nerve palsy)	72
Negative allergy tests (to exclude allergic causes)	27
Blood tests for indications of infection (e.g. neutrophils)	38
2) Should the following clinical signs/changes in examinations be included as an indication of an otologic exacerbation?	
Perforated eardrum	62
Ear discharge	92
Nystagmus	35
Signs of otitis media in otoscopy (i.e. erythema, collection)	92
Pathologic tympanometry findings	50
Signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy)	69
Impaired hearing tested by pure-tone audiometry (air and bone-conduction)	69
Positive microbiology culture from ear discharge	46
Blood tests for indications of infection (e.g. neutrophils)	23

Clinical signs/examinations in red were ranked as the most important in their category.

Table S5: Responses to key questions of eDelphi survey 3 regarding highly voted items that have not reached consensus on previous rounds

	% of agreement
1) Should changes in the following symptoms be included as an indication of a sinonasal exacerbation?	
Reduced QoL evaluated by any sinonasal specific QoL questionnaire	50
Decreased sense of smell	58
Headache	42
Bad sleep	15
Cough	15
2) Should the following clinical signs/changes in examinations be included as an indication of a sinonasal exacerbation?	
Erythema or oedema of nasal mucosa	46
Appearance or swelling of nasal polyps	46
Signs of acute complication (e.g. orbital infection or abscess, meningitis, cerebral infection, cranial nerve palsy)	52
3) Should changes in the following symptoms be included as an indication of an otologic exacerbation?	
A feeling of fullness in the ears	58
4) Should the following clinical signs/changes in examinations be included as an indication of an otologic exacerbation?	
Perforated eardrum	54
Pathologic tympanometry findings	38
Signs of acute complication (mastoiditis, meningitis, cerebral abscess, facial or other cranial nerve palsy)	46
Impaired hearing tested by pure-tone audiometry (air and bone-conduction)	62
Pathologic pneumatic otoscopy	35

QoL: quality of life.