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The Impact of Elexacaftor/Tezacaftor/Ivacaftor on Sinus Disease, Olfaction, and the Sinonasal Microbiome in Patients with Cystic Fibrosis

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ABSTRACT

Background: Elexacaftor/tezacaftor/ivacaftor (ETI) is a highly effective triple modulator therapy that has significantly reduced morbidity and mortality in patients with cystic fibrosis. Beyond pulmonary improvements, ETI's impact on sinus disease, olfactory function, and the sinonasal microbiome is just beginning to be understood. We present a contemporary review of sinonasal changes in patients with cystic fibrosis after ETI initiation.

Methods: We conducted a literature review using PubMed and Google Scholar. Articles about ETI's impact on sinonasal disease and symptoms in patients with cystic fibrosis published in English from 2019 to August 2024 were eligible for inclusion. Studies were selected based on their contribution to understanding changes in sinus disease severity, sinonasal quality of life, olfactory function, and the sinonasal microbiome in patients with cystic fibrosis after starting ETI.

Results: An initial query yielded 41 articles. After screening abstracts, 23 articles were chosen for further review. A total of 19 articles met full inclusion and exclusion criteria. Evidence suggests ETI significantly improves sinus disease in patients with cystic fibrosis, with clinical, radiographical, and quality of life improvements observed within days to months and persisting for up to two years. Studies on olfactory changes showed mixed results, with persistent dysfunction demonstrated on psychophysical tests despite subjective improvements. ETI also alters the sinonasal microbiota, by reducing pathogenic bacteria and total bacterial load, though the clinical implications remain under investigation.

Conclusions: ETI therapy markedly improves both objective evidence of sinus disease and sinonasal quality of life in patients with cystic fibrosis. Despite some improvements in olfactory dysfunction, objective tests consistently report refractory impairment post-ETI. Changes in the sinonasal microbiome are evident, but dysbiosis remains a concern. Further research is needed to clarify the long-term effects of ETI on olfactory dysfunction and the sinonasal microbiome, especially in younger populations.

1. Background

1.1 OVERVIEW

Cystic fibrosis (CF) is a rare, autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Advances in care have led to the development of CFTR modulators, and most recently elexacaftor/tezacaftor/ivacaftor (ETI) a highly effective triple modulator therapy. While ETI has greatly improved outcomes, most studies have focused on the pulmonary benefits. This article will provide an overview of ETI's impact on sinus disease, olfaction, and the sinonasal microbiome.

1.2 CYSTIC FIBROSIS AND ELEXACAFTOR/TEZACAFTOR/IVACAFTOR

CF affects an estimated 89,900-100,000 people globally. Over 2000 mutations in CFTR have been identified, with the F508del variant present in ~85% of U.S. patients with CF[1]. Until the early 2010s, CF care focused on slowing lung disease progression (the most frequent cause of mortality and morbidity) with inhaled and systemic antibiotics, physiotherapy, and inhaled medications to improve mucus clearance. In 2012, CFTR modulators were introduced, offering targeted therapies to improve protein folding and intracellular trafficking[2].

ETI, marketed as Trikafta and Kaftrio, is the most effective CFTR modulator. Approved by the U.S. Food and Drug Administration (FDA) in 2019 for patients aged 12 and older with at least one F508del allele[3], its indications have since expanded to children as young as two. Elexacaftor and tezacaftor increase functional CFTR protein at the cell surface, while ivacaftor enhances activity, improving anion transport across the membrane[4]. Additionally, ETI has since been studied and approved for patients with at least one copy of over 170 rare CFTR mutations that have demonstrated responsiveness, further expanding eligibility[5,6]. ETI has significantly reduced CF-related morbidity and mortality, leading to fewer acute pulmonary exacerbations, improved lung function (e.g., forced expiratory volume in one second [FEV1]), increased body mass index (BMI), increased life expectancy, and improved quality of life[3,5,7-10]. Although most studies have focused on pulmonary outcomes since the introduction of ETI, CF is a multisystem disease. Consequently, research into ETI's effects on sinonasal symptoms has progressed. For a comprehensive review of the pulmonary improvements following ETI initiation, see Ong et al. (JAMA 2023)[1].

1.3 SINUS DISEASE IN CYSTIC FIBROSIS

Chronic rhinosinusitis (CRS) is defined by persistent inflammation of the sinonasal mucosa for 12 weeks or more[11]. Diagnosis requires evidence of disease on endoscopy or imaging and symptoms (e.g. nasal congestion, anterior or posterior nasal drainage, facial pain or pressure, reduced sense of smell). In CF, defective ion transport leads to thickened secretions that overwhelm mucociliary clearance, mucus stasis, persistent infections, and mucosal inflammation[12,13]. Nearly all patients with CF exhibit sinonasal inflammation and infection on imaging or endoscopy (CF-CRS)[14]. Otolaryngologists evaluate sinus disease using endoscopic and radiographic scoring systems (Table 1).

1.4 SINONASAL QUALITY OF LIFE IN PATIENTS WITH SINUS DISEASE

Patient reported outcome measures are important for assessing and monitoring sinonasal quality of life (QoL) i.e., the impact of sinonasal conditions on a patient's overall well-being and daily functioning[15]. Surveys such as the 22-item sinonasal outcome test (SNOT-22), capture symptom burden and have been validated in large cohorts of patients, including those with CF. Recent work has identified the minimal clinically important difference (MCID) for SNOT-22 scores in cystic fibrosis, further enhancing its clinical utility[17]. Table 2 outlines common instruments used to evaluate sinonasal quality of life.

Table 1: Objective Scoring Systems for the Assessment of Sinus Disease

Name	Description	Additional Considerations
Nasal Polyp Score (NPS)	-Endoscopic assessment of the size and extent of nasal polyps -Each side is scored on a scale of 0 (no polyps) to 4 (large polyps that completely obstruct the nasal cavity) -Total score is the sum of both nostrils, ranging from 0-8	-Useful for evaluating the severity of nasal polyposis specifically and monitoring changes over time -Easy to perform during routine endoscopic examinations
Lund-Kennedy Score and Modified Lund-Kennedy Score (mLKS)*	-Evaluates the presence of polyps, edema, scarring/crusting, and discharge within the nasal cavity and sinuses -Each parameter is scored on a scale of 0-2, with higher scores indicating more severe pathology -Total score ranges from 0-12 *The mLKS excludes the crusting/scarring parameter for increased reliability	-High inter-rater and test-retest reliability[15] -Most widely used clinical scoring system for sinonasal disease
Lund-Mackay Score (LMS)	-CT-based scoring system that assesses the extent of sinus opacification -Each sinus (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal) is scored on a scale from 0 (no opacification) to 2 (complete opacification) -The osteomeatal complex (OMC) is scored separately as either 0 (not obstructed) or 2 (obstructed) -Total score ranges from 0-24	-High inter- and intra-observer reliability -Useful for planning surgical interventions and monitoring response to treatment[15] -Evidence that there is little association between radiologic grade and subjective measures of sinonasal quality of life[16]

Table 2: Common Patient Reported Outcome Measures to Evaluate Sinonasal Quality of Life

Name (Abbreviation)	Description	Additional Considerations
Sinonasal Outcome Test (SNOT-22)	-A 22 item survey to assess the impact of sinusitis on QoL -Covers physical, functional, and emotional aspects of CRS -Each item is scored from 0-5, with higher scores indicating worse symptoms and QoL	-Widely used -Easy to administer -MCID of 8.5 in patients with CF[17]
Rhinosinusitis Disability Index (RSDI)	-A 30-question survey that covers physical, functional, and emotional domains -Each item is scored from 0-4, with higher scores indicating worse symptoms and QoL	-Used for a more detailed evaluation of rhinosinusitis-related disability
Rhinosinusitis Quality of Life Survey (RQLQ)	-A 28-question survey divided into 7 domains including activity limitations, sleep problems, non-nose/eye symptoms, and practical problems -Items are scored on a 7-point scale (0=not impaired at all, 6=severely impaired)	-Translated into multiple languages -One-week recall period

1.5 OLFACTORY DYSFUNCTION IN CYSTIC FIBROSIS

Patients with CF are more likely to have olfactory dysfunction (OD) than age-matched controls[18]. While up to 75% of patients report normal smell, objective tests show 60-95% have some degree of impairment[19–21]. OD impacts quality of life, safety (e.g. reduced ability to detect hazards like smoke), and BMI. Assessment methods include subjective tools, such as olfactory quality of life surveys, and objective tests like the Sniffin' Sticks Identification Test, a validated psychophysical instrument (Table 3).

Table 3: Assessment Methods to Evaluate Olfactory Dysfunction

Type	Example, Description	Considerations
Patient Surveys (subjective)	Questionnaire of Olfactory Disorders (QOD) -Consists of various statements related to domains of daily life (e.g. food enjoyment, detecting hazards, and social interactions) -Patients rate these statements, providing a quantitative measure of the severity of their OD and its impact on QoL	-Evaluates olfactory-specific quality-of-life measures -MCID of approximately 3.7[22]
	Visual Analog Scale (VAS) -Patients mark a point on a continuous line that represents their perception of olfactory function -The line typically ranges from 'no sense of smell' to 'excellent sense of smell' -Provides a simple, quick, and subjective measure of olfactory function	-Useful for tracking changes over time and assessing treatment outcomes -Has demonstrated a strong correlation with objective tests of OD[22]
Psychophysical Testing	Sniffin' Sticks Identification Test (SSIT) -Consists of three components: threshold, discrimination, and identification	-Objective gold-standard for psychophysical olfactory testing
	University of Pennsylvania Smell Identification Test (UPSIT) -Also known as the 40-question smell identification test (SIT) -Patients are asked to identify a set of standardized odorants in 4 booklets	-Objective measure of odor identification

2. Methods

A literature review was conducted to evaluate the effects of elexacaftor/tezacaftor/ivacaftor (ETI) in sinus disease and sinonasal quality of life, olfactory function, and the sinonasal microbiome in patients with cystic fibrosis. PubMed, MEDLINE, and Google Scholar databases were searched for articles published between January 2019 and August 2024. The following search terms were used in various combinations: "elexacaftor," "tezacaftor," "ivacaftor," "CFTR modulator(s)," "cystic fibrosis," "sinonasal microbiome," "olfaction," "olfactory dysfunction," "olfactory impairment," "ETI," "HEMT," "olfaction," "microbiome," "chronic rhinosinusitis," "sinus disease," and "quality of life." Inclusion criteria for this review were: articles published in English, research involving patients with cystic fibrosis treated with ETI, and articles addressing chronic rhinosinusitis, sinonasal quality of life, olfactory dysfunction, and the microbiota of the upper respiratory tract. Exclusion criteria included non-peer-reviewed articles, studies lacking specific sinonasal findings, studies using non-original cohorts, case reports, and abstracts accepted to conference presentations without accompanying articles.

3. Analysis of Findings

3.1 ARTICLE SELECTION

The initial query yielded 41 eligible articles. After screening abstracts, 23 articles met initial inclusion

criteria and were chosen for further review. After review by two independent researchers and applying full inclusion and exclusion criteria 19 articles were selected for final synthesis. A total of 4 articles were excluded from analysis for failing to meet full predetermined inclusion and exclusion criteria (e.g. non-original cohort, reviews, case studies). The data were organized into four primary focus areas: (1) changes in sinonasal QoL, (2) objective (radiographic and endoscopic) evidence of disease, (3) changes in olfaction, and lastly (4) changes in sinonasal microbiome after ETI initiation. For studies with overlapping focus areas, one was arbitrarily chosen. If multiple focus areas were discussed, the study was repeated in discrete tables with applicable findings. Tables 4, 5, 6, and 7 are organized by article (first author and year), cohort size, data collection timepoints, instrument(s) used, and notable findings.

3.2 THE IMPACT OF ETI ON SINONASAL QUALITY OF LIFE OUTCOME MEASURES

Several studies have documented the benefits of ETI (and other CFTR modulators) on sinonasal quality of life in patients with cystic fibrosis (PwCF). Five studies were selected for inclusion in Table 4 and for discussion. In 2021, DiMango et al. published the first prospective cohort study of patients with CF on ETI, reporting a clinically significant improvement in SNOT-22 scores after three to six months of treatment[23]. Studies have shown that patients homozygous for F508del and with higher baseline SNOT-22 scores experience the most significant improvements with ETI[17]. Tham, Li et al. recently conducted a meta-analysis of seven prospective and two retrospective studies (249 PwCF), showing significant improvements in SNOT-22 scores after ETI treatment[24]. Clinically significant improvements in sinonasal quality of life have also been reported as early as one week after treatment initiation[25]. Additionally, Shakir et al. reported a statistically and clinically significant improvement in SNOT-22 scores after six months of ETI in a longitudinal cohort study of 32 patients[26]. Collectively, these studies demonstrate a consistent and clinically significant improvement in sinonasal quality of life after ETI initiation, particularly among patients with higher baseline disease burdens.

Table 4: Studies on Sinonasal Quality-of-Life before and after ETI Initiation

Article	Cohort	Timepoints	Instrument	Findings
DiMango (2021)[23]	-n=43	-Baseline -3 months after ETI initiation	-SNOT-22 -CFQ-R	-Significant improvement in nearly all domains of the SNOT-22 and CFQ-R
Shakir (2022)[26]	-n=32	-Baseline -6 months after ETI initiation	-SNOT-22	-Median SNOT-22 fell from 36.5 to 20 ($p<0.001$)
Beswick (2024)[27]	-n=30 -n=25	-Baseline -6 months after ETI initiation	-SNOT-22	-Baseline: mean SNOT-22 score of 33.1 -Follow-up: mean SNOT-22 score improved by 15.3 ($p<0.007$)
Stapleton (2022)[25]	-n=27	-Baseline -Days 7 and 28 -Months 2, 4, 6, and 9 -Second visit between 6-12 months after ETI initiation (median 9 months)	-SNOT-22	-Median SNOT-22 score improved from a median of 21 to a median of 18 -Significant improvements in SNOT-22 scores seen by day 7 -Persistent improvement seen to 180 days ($p<0.0001$)
Douglas (2021)[28]	-n=25	-Varied (retrospective), mean follow up of 5 months	-SNOT-22	-SNOT-22 improved by 10.2 points at average follow up time

Bode (2023)[29]	-n=43 -n=20 (control group)	-Mean of 9.3 (2-16) months after ETI initiation	-SNOT-22	-SNOT-22 improved from mean of 32.7 to mean of 15.7 (p<0.0001) post-ETI -Children showed lower SNOT-22 scores than adults and SNOT-22 score improved from 9.4 to 2.2 (p=0.25)
Allgood (2023)[30]	-n=22	-Baseline -Days 14, 28, 42, 56, 70, and 84 after ETI initiation	-SNOT-22	-Baseline mean of 21.7, which improved to 13.8 at the 12-week (84 day) time point -Largest drop in mean SNOT-22 score from baseline to day 14
Minzoni (2024)[31]	-n=45	-Baseline -12 months after ETI initiation	-SNOT-22	-Mean SNOT-22 reduced from 53.9 to 22.8 (p<0.001) -Subgroup analysis showed a statistically significant greater reduction in scores among post-ESS patients (-19.6 vs -35.8, p=0.015)
Tervo (2023)[32]	-n=41	-Baseline -3 months after ETI initiation	-CFQR -SNOT-22	-SNOT-22 and CFQR scores significantly improved in cohort after ETI (p=<0.0001)

3.3 THE IMPACT OF ETI ON OBJECTIVE MEASURES OF SINUS DISEASE

Multiple studies have demonstrated objective improvements in sinus disease after ETI initiation. Han et al. observed a reduction in the frequency of rhinology clinic visits and nasal cultures obtained[33]. Bode et al. noted improvements in endoscopic exams in 5 out of 8 patients within one year of ETI initiation[29]. Stapleton et al. noted significant improvement in polyps, crusting, and inflammation on endoscopic exams, with a reduction in sinus disease severity seen in over thirty patients[25]. Lastly, Minzoni et al. documented significant improvements across multiple parameters, reflecting a comprehensive improvement in sinonasal outcomes at the one-year mark post-ETI initiation[31]. These findings highlight ETI's role in improving markers of sinus disease, including endoscopic findings and healthcare utilization indices.

Table 5: Studies on Objective Evidence of Sinus Disease before and after ETI Initiation

Article	Cohort	Timepoints	Instrument	Findings
Han (2024)[33]	-n=126	-Baseline -12 months after ETI initiation	-Frequency of rhinology clinic visits and nasal cultures obtained -Rate of sinus surgery	-Decreased clinic visits and fewer nasal cultures obtained -No significant change in the number of sinus surgeries performed
Bode (2023)[29]	-n=8 with exam -n=20 (control group)	-Mean of 9.3 (2-16) months after ETI initiation	-NPS	-Clinical improvement seen in 5/8 patients on endoscopic exam (e.g. NPS scores)
Stapleton (2022)[25]	-n=34	-Baseline -Second visit 6-12 months after ETI initiation (median 9 mo.)	-LMS -mLKS	-Improved endoscopic findings (e.g. polyps, crusting, and visible inflammation) -Improved radiographic evidence of CF-CRS

Minzoni (2024)[31]	-n=45	-Baseline -12 months after ETI initiation	-NPS -mLKS -LMS	-NPS reduced from 1.0 to 0.7 (p=0.015) -mLKS decreased from 4.9 to 2.4 (p<0.001) -LMS decreased from 15.8 to 6.7 (p<0.001)

3.4 THE IMPACT OF ETI ON OLFACTORY DYSFUNCTION

Studies on the effect of ETI therapy on olfactory dysfunction (OD) in patients with cystic fibrosis have focused predominantly on adults and yielded mixed conclusions. Five studies were identified with outcome measures evaluating OD (Table 6). Subjective olfactory quality of life scores show statistically significant improvements but are not always clinically relevant. Miller et al. contributed to our understanding of smell loss in patients with CF by noting a MCID of 3.7 on the QOD[22]. Findings suggest that persistent olfactory impairment following ETI treatment may result from irreversible olfactory neuron loss in the setting of chronic inflammation. We agree with the importance of objective, psychophysical testing for evaluating OD in patients with cystic fibrosis. We also emphasize the value of further studies, especially with pediatric patients, to assess the effects of early ETI initiation. Notably, although ETI has proven benefits in sinonasal-related quality of life, it does not appear to enhance olfactory-related quality of life metrics.

Table 6: Studies on Olfactory Function before and after ETI Initiation

Article	Cohort	Timepoints	Instrument	Findings
Miller (2024)[34]	-n=26	-Baseline -6 months -24 months	-UPSIT -QOD-NS -Olfactory cleft opacification (%OCO)	-UPSIT scores worsened after ETI -%OCO remained stable -QOD-NS improved significantly from baseline to 6 months and remained significant at 24-month follow-up
Miller (2024)[22]	-n=65	-Baseline -3-6 months after ETI	-QOD	-QOD score improved significantly but did not exceed the MCID -Participants with worse baseline clinical scores and nasal polyps did have a clinically significant improvement in QOD
Beswick (2022)[35]	-n=30 -n=25	-Baseline -6 months	-UPSIT -QOD -% OCO	-At baseline, cohort was hyposmic (mean SIT 31.3), had significant %OCO (mean 65.6%), and non-impaired olfactory QOL (mean QOD 6.1) -Mean UPSIT mildly worsened (p=0.009), mean %OCO remained stable (p=0.46), and mean QOD improved modestly (p=0.008)
Bacon (2022)[21]	-n=34 -n=28	-Baseline -Single follow up (6-12 months after initiation)	-UPSIT	-High prevalence of OD among PwCF at baseline (74.6%) -No improvement in UPSIT scores after at least 6 months of ETI
Minzoni (2024)[31]	-n=45	-Baseline -12 months after ETI initiation	-VAS -SSIT	-VAS dropped from 3.7 to 2.6 (p=0.034) -Mean SSIT increased from 9.6-12.3 (+2.7, p=0.002)

3.5 THE IMPACT OF ETI ON THE SINONASAL MICROBIOME

The initiation of ETI has been shown to significantly alter the sinonasal microbiome, leading to notable shifts in bacterial populations and highlighting the interconnectedness of sinonasal and pulmonary health in cystic fibrosis. Zemke et al. demonstrated that ETI initiation is associated with notable changes in the sinonasal microbiome, including a reduction in the abundance of pathogenic bacteria, particularly *Pseudomonas aeruginosa*, and an increase in bacteria associated with healthy sinonasal environments, such as *Moraxella*. Additionally, they noted that existing evidence shows that patients with CF may be colonized with a greater proportion of Staphylococcus spp. in the sinuses compared to the lungs.

Armbruster et al. corroborated these findings, showing a reduction in the relative abundance of *P. aeruginosa* after ETI initiation, although the same clonal populations persisted. This persistence indicates that while ETI reduces bacterial load, it may not fully eradicate pathogenic strains. This underscores the need for continued otolaryngologic care and suggests that the nasal cavity and sinuses could serve as alternative sites to monitor respiratory microbes, population diversity, and disease status. Another study found that ETI led to a significant reduction in *Pseudomonas* spp., with Staphylococcus spp. (including methicillin-resistant staphylococcus aureus) becoming the dominant organisms in the cohort of patients. Hilliam et al. found that *Pseudomonas* spp. levels within the sinuses dropped sharply after ETI initiation but rebounded over time, with data extending up to two years post-ETI. This finding mirrors what was previously shown in lower respiratory studies, again reinforcing the similarities between findings in pulmonary and sinonasal microbiome studies. Future directions could explore sinonasal microbiome changes beyond two years of ETI treatment, assess whether ETI reduces the need for antibiotics in treating chronic sinus disease, and examine the potential of adjunctive therapies to further address sinonasal dysbiosis in cystic fibrosis.

Table 7: Studies on the Sinonasal Microbiome before and after ETI Initiation

Article	Cohort	Timepoints and Samples	Instrument	Findings
Atteih (2024)[36]	-n=18	-Pre- and post-ETI initiation samples (baseline, 1 months, 3 months, and 6 months) -Paranasal sinus samples collected under endoscopic exam	-Tested for cytokines, minerals, and other biomarkers	-ETI use seems to result in decreased inflammatory signals and reduced microbial nutrients within the upper respiratory tract
Zemke (2024)[37]	-n=23	-Paired pre- and post-ETI (median 9 months) -Sinonasal samples collected under endoscopic exam	-Analyzed with 16s PCR to measure total bacterial abundance	-Reduction in *Pseudomonas* bacterial load within patients colonized with *Pseudomonas* at baseline -Relative abundance of *Moraxella* increased after ETI
Armbruster (2024)[38]	-n=19	-Pre- and post-ETI initiation (median 372 days) -Sinus, throat, and/or sputum samples collected	-16s rRNA gene amplicon sequencing -Species-specific sequencing -Whole population genomic sequencing -Phylogenomic analyses	-Total bacterial load lower after ETI -Lower relative abundance of *P. aeruginosa*, though remained detectable in most participants -Same strain of *P. aeruginosa* persists after ETI

Hilliam (2024)[39]	-n=38	-Pre- and post-ETI initiation -Sinus swabs from middle meatus	-16s and custom amplicon sequencing to characterize sinus microbiota	-Reduction in abundance of *Pseudomonas* after ETI -*Staphylococcus* (including MRSA) became dominant in 37 of the participants -No change in overall bacterial load
Armbruster (2022)[40]	-n=27	-Pre- and post-ETI initiation (median 522 days) -Swabs collected from paranasal sinuses -Sinus wash effluent collected for cytokine analysis	-16s rRNA gene sequencing -Cytokine analyses -Bacterial culturing	-Worsened sinus disease is associated with reduced microbial community diversity -Higher Shannon or Simpson diversity predicted decreased proinflammatory cytokine IL-1B levels

4. Conclusions

4.1 ETI's IMPACT ON SINUS DISEASE IN PATIENTS WITH CYSTIC FIBROSIS

ETI initiation is associated with significant improvements in sinus disease, as reflected by numerous studies reporting clinically meaningful improvements in sinonasal quality of life scores. Patients with higher baseline (worse) SNOT-22 scores and who had homozygous F508del genotypes, seem to experience the most pronounced benefits. Additionally, evidence supports ETI improves the clinical appearance and severity of sinus disease. More broadly, ETI initiation was associated with fewer clinic visits and nasal cultures obtained in an observational study, suggesting improvements in sinus disease severity in a particular cohort. Combining ETI with sinus surgery shows promise, particularly in cases of refractory sinus disease and post-lung transplantation, though larger studies are needed to further characterize these benefits. Pediatric and adolescent populations appear to be underrepresented in current studies on the impact of ETI on sinonasal disease, olfactory dysfunction, and the sinonasal microbiome.

4.2 ETI's IMPACT ON OLFACTORY DYSFUNCTION IN PATIENTS WITH CYSTIC FIBROSIS

Studies on the impact of ETI on olfactory dysfunction in cystic fibrosis have shown mixed results. Subjective measures often indicate improvements in perceived olfactory function and olfactory-related quality of life after ETI initiation; however, studies with psychophysical olfactory tests generally show little to no improvement post-ETI. This suggests that olfactory dysfunction may persist due to irreversible damage to olfactory neurons, emphasizing the need for continued research on the pathophysiology of smell loss in patients with cystic fibrosis and the potential benefits of earlier ETI initiation.

4.3 ETI's IMPACT ON THE SINONASAL MICROBIOME IN PATIENTS WITH CYSTIC FIBROSIS

Research on the sinonasal microbiome before and after ETI has shown significant shifts in bacterial loads and diversity. ETI initiation is associated with a reduction in pathogenic bacteria and an increase in beneficial populations. Despite reductions in total bacterial load, the persistence of the same strains of *P. aeruginosa* suggests that ETI does not fully eliminate native pathogenic strains. *Staphylococcus* spp. tend to become more dominant after ETI initiation, mirroring previous pulmonary microbiome findings. Future research may explore the long-term effects of ETI on sinonasal microbiome stability, its impact on antibiotic use, and overall management of sinus disease in patients with cystic fibrosis.

Conflicts of Interest Statement:

The authors have no conflicts of interest to disclose.

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