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Use of inhaled antibiotics among Danish patients with cystic fibrosis

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Abstract

Background: Inhaled antibiotics are an important part of cystic fibrosis (CF) airway disease management and should be individualized to fit the microorganism and match patient needs. To investigate the implementation of personalized treatment, this study mapped the use of different types of inhaled antibiotics and adherence patterns.

Methods: We performed individual structured interviews in a cross-sectional study at the CF Centre in Copenhagen, Denmark. Patients with CF older than 15 years attending clinical consultations were included. Clinical data were obtained from centralized databases.

Results: Among 149 participants, 107 (72%) had indication for treatment with inhaled antibiotics. In this group, 97 (91%) reported the use of inhaled antibiotics within the last 12 months. Change from one inhaled antibiotic to another during that period was reported by 31 (29%), and 17 (25%) with *Pseudomonas aeruginosa* had used off-label antibiotics. Adherence to a minimum of one daily dose of antibiotic was reported by 78%, while adherence to all daily doses was 28 percentage points lower. Skipping inhalations was due to side effects and doubt about the effect in less than 5% of cases.

Conclusion: Change of inhaled antibiotics and use of off-label antibiotics for inhalation were common and side effects were a rare cause of nonadherence. This suggests satisfactory implementation of the principle of tailored antibiotic inhalation prescription in the Copenhagen CF population. Adherence to at least one daily inhalation dose was markedly higher than adherence to multiple daily inhalations.

KEYWORDS
adherence, compliance, inhalation, nebulized

1 | INTRODUCTION

Chronic lung infection is a major concern in patients with cystic fibrosis (CF). Inhaled antibiotics are recommended as eradication therapy in early colonization and as suppressive treatment for chronic infections,[1] although guidelines for treatment with inhaled antibiotics vary between countries.

In current American guidelines, tobramycin remains the drug of choice for suppressive therapy in chronic infection with *Pseudomonas aeruginosa*, with aztreonam as the only recommended alternative.[2] A 2012 European consensus paper proposed colistin as equivalent to tobramycin, and highlighted the potential of several new drugs for inhalation treatment, such as amikacin liposomal suspension.[1] American and European guidelines agreed that personalized treatment is necessary due to factors such as resistance pattern, patient preference, poor adherence, and adverse events.[1,2] Moreover, the CF treatment regime has become more comprehensive over the decades, emphasizing the importance of tailored treatment to reduce the overall burden of nebulized treatment, which is particularly demanding.[3,4]

All patients with chronic lung infection are recommended continuous therapy with inhaled antibiotics at the Copenhagen CF Centre. Inhaled colistin is first-line treatment for both initial and chronic *P. aeruginosa* infection.[5] Second-line treatment is inhaled tobramycin, while aztreonam, meropenem (off-label), or ceftazidime (off-label) can be used for recurring *P. aeruginosa*.[5] Furthermore, levofloxacin, amikacin (off-label), imipenem (off-label), and piperacillin/tazobactam (off-label) are used for inhalation treatment in the clinic. The same drugs are used in the systematic treatment of *Burkholderia* spp., *Achromobacter* spp., and clinically relevant *Mycobacterium* spp. Some of the off-label inhalation drugs are intravenous solutions administered by a nebulizer, which are tested for inhalation use in the Copenhagen CF Centre. For administration of inhaled solutions, most patients use devices with vibrating mesh technology,[6] though jet nebulizers are used for ceftazidime and amikacin inhalations. In recent years, inhaled powder antibiotics as replacement or supplement to nebulized treatment have won ground after reports of increased adherence and patient satisfaction with equivalent clinical effects.[7,8]

Low medication adherence in CF populations has been reported in studies from the US,[9] UK,[10] France,[11] and Denmark,[12] and some reports show that this particularly applies to inhaled medications.[4,11] Other studies have found correlations between adherence and clinical outcomes,[9,13] for example, Eakin et al. found associations between low medication possession ratio, higher frequency of pulmonary exacerbations, and lower forced expiratory volume in the first second in percent predicted ($FEV_1\%$).[14] Thus, adherence appears to be of clinical importance, yet determinants of adherence to inhaled medications have not been systematically studied.

We hypothesized that tailored prescription according to local guidelines leads to a high coverage and a wide distribution of on and off label inhaled antibiotics at the Copenhagen CF Centre. Further, we speculated that adherence to inhaled antibiotics was challenged by the disadvantages and side effects of inhalation therapy and that elucidating potential barriers to adherence could guide optimized treatment strategies. To improve our understanding of patterns of inhaled antibiotic use, this study describes the use of different types of inhaled antibiotics against pathogenic Gram-negative bacteria at the Copenhagen CF Centre. We explored the implementation of local guidelines and investigated trends in adherence patterns.

2 | MATERIALS AND METHODS

2.1 | Study design

This cross-sectional study, based on individual structured interviews,[15] was carried out in the Copenhagen CF cohort from October 2020 to January 2021. Interviews were carried out in person or by telephone. All interviews were performed by the same person, who was not part of the CF multidisciplinary team.

2.2 | Participants

All patients over the age of 15 years followed at the Copenhagen CF Centre were eligible for participation. Patients were identified via the Danish Cystic Fibrosis Patient Registry and were invited to the study at their routine clinical consultations. A subgroup for further analyses (study group) was formed, including all patients infected with either *P. aeruginosa*, *Burkholderia* spp., *Achromobacter* spp., or clinically relevant *Mycobacterium* spp.[1] during the 12 months covered by the interview (Supporting Information: Figure 1). Lung transplanted patients were excluded from this group. These criteria were identical to our local recommendations for continuous treatment with inhaled antibiotics.

2.3 | Questionnaire

A questionnaire covering various aspects, including adherence of inhaled antibiotic use during the previous 12 months was designed for the study. Supporting Information regarding antifungal and nonantibiotic inhalations (i.e., dornase-alpha, hypertonic saline, mannitol, short- and long-acting asthma inhalations, and inhaled steroids) was gathered. Antifungal treatment is not included as antibiotic treatment in this study. Questions were read aloud, and the patients answered without knowing the answer options. Answers were categorized in an answer option or entered in a narrative format by the interviewer. Narrative answers were added to existing categories or divided into newly formed categories after the end of data collection[15] (Supporting Information: Table 1). To minimize recall bias,[16] only patients who had used inhaled antibiotics within three months were asked about adherence. Adherence questions included a global recall of adherence over the past 12 months as well as adherence in the previous month in absolute numbers of inhaled

doses (Supporting Information: Table 2). A satisfying level of adherence was defined as always or almost daily inhaling. The intended number of daily inhalations was obtained from the participants. Adherence in percentage was subsequently calculated, with a maximum allowed adherence at 100%.[17] For statistical analyses on adherence data, patients who reported no use of inhaled antibiotics were placed in the lowest adherence category, and patients with infections eradicated more than three months before the interview were excluded. To mitigate overestimation, adherence questions were preceded by ensuring the participant that nonadherence is common among persons with CF.

2.4 | Other data

Demographic and clinical data including bacteriology and lung function measures (FEV$_1$%) was obtained from The Danish Cystic Fibrosis Patient Registry. Lung function tests (Intramedic Vyntus^{TM} SPIRO, reference: Standard EU-GLI[18]) and sputum samples for microbiological examination are collected monthly at routine consultations. Microbiological cultures and antibiotic susceptibility data were obtained for 2019 and 2020 from the clinical microbiology database. The use of inhaled antibiotics was stratified by in vitro susceptibility using the first and the latest positive culture of each bacteria in the period between January 1st, 2019 and study inclusion.

2.5 | Statistical analysis

All statistical analysis was performed in R for Windows v 3.6.0 (interface: RStudio v 1.2.5001). Statistics were primarily descriptive, and data were presented as count (percentage) or median (interquartile range [IQR]; Tables 1–2 and Figures 1–3). For key findings, confidence

TABLE 1 Baseline data of 149 participants with CF

	All (n = 149)	Study group[a] (n = 107)	No indication for inhaled antibiotics[b] (n = 42)
Demographics			
Female, n (%)	71 (48)	48 (45)	23 (55)
Age groups (years), n (%)			
15–17	9 (6)	3 (3)	6 (14)
18–24	36 (24)	24 (22)	12 (29)
25–34	41 (28)	29 (27)	12 (29)
≥35	63 (42)	51 (48)	12 (29)
Lung disease			
FEV$_1$%, median (IQR)	78 (52–95)	71 (48–89)	92 (70–104)
Lung transplanted, n (%)	6 (4)	0 (0)	6 (14)
Mutation			
Severe mutation (Class I–III), n (%)	135 (91)	101 (94)	34 (81)
Mild mutation (Class IV–VI), n (%)	14 (9)	6 (6)	8 (19)
Work (hours per week), n (%)			
0	31 (21)	20 (19)	11 (26)
1–15	17 (11)	15 (14)	2 (5)
16–29	21 (14)	14 (13)	7 (17)
≥30	80 (54)	58 (54)	22 (52)
Treatment time (min/day)			
Time spent on inhaled medication: median (IQR)	30 (10–60)	45 (20–90)	10 (3–30)

[a]Infected with *P. aeruginosa*, *Achromobacter* spp., *Burkholderia* spp., or *Mycobacterium abcsessus*, or other clinically relevant mycobacteria with an antibiotic treatment indication, within 12 months before study inclusion.

[b]According to the local guidelines.

TABLE 2 Inhalation patterns of 149 participants with cystic fibrosis

	Study group[a] (n = 107)		No indication for inhaled antibiotics[b] (n = 42)	
	n	% (95% CI[c])	n	% (95% CI[c])
Use of inhaled medications				
Inhaled antibiotics within recent 12 months	97	91 (83–95)	12[d]	29 (16–45)
Inhaled antibiotics within recent 3 months	91	85 (77–91)	6	14 (6–29)
Nonantibiotic inhalations within recent 12 months[e]	104	97 (91–97)	38	90 (76–97)
Antibiotic inhalation regime within recent 12 months[f]				
Unaltered	58	54 (44–64)	12	29 (16–45)
≥1 Change	31	29 (21–39)	0	0 (0–10)
Alternating regularly	8	7 (3–15)	0	0 (0–10)
None	10	9 (5–17)	30	71 (55–84)
Prescription practice of inhaled antibiotics				
Use within recent 12 months despite known resistance	30	28 (20–38)	0	0 (0–10)
Current use despite resistance in most recent culture	23	21 (14–31)	0	0 (0–10)
Number of different inhaled antibiotics ever used[f]				
0	0	0 (0–0)	12	29 (16–45)
1–2	33	31 (22–41)	23	55 (39–70)
3–5	59	55 (45–65)	7	17 (7–32)
≥6	15	14 (8–22)	0	0 (0–0)

[a]Infected with *P. aeruginosa*, *Achromobacter* spp., *Burkholderia* spp., or *Mycobacterium abcsessus*, or other clinically relevant mycobacteria with an antibiotic treatment indication, within 12 months before study inclusion.
[b]According to local guidelines.
[c]CI, confidence interval (95% confidence level).
[d]Indication for treatment with inhaled antibiotics not included in local guidelines.
[e]Antifungal therapy, dornase-alpha, hypertonic saline, mannitol, asthma inhalations, and inhaled steroids.
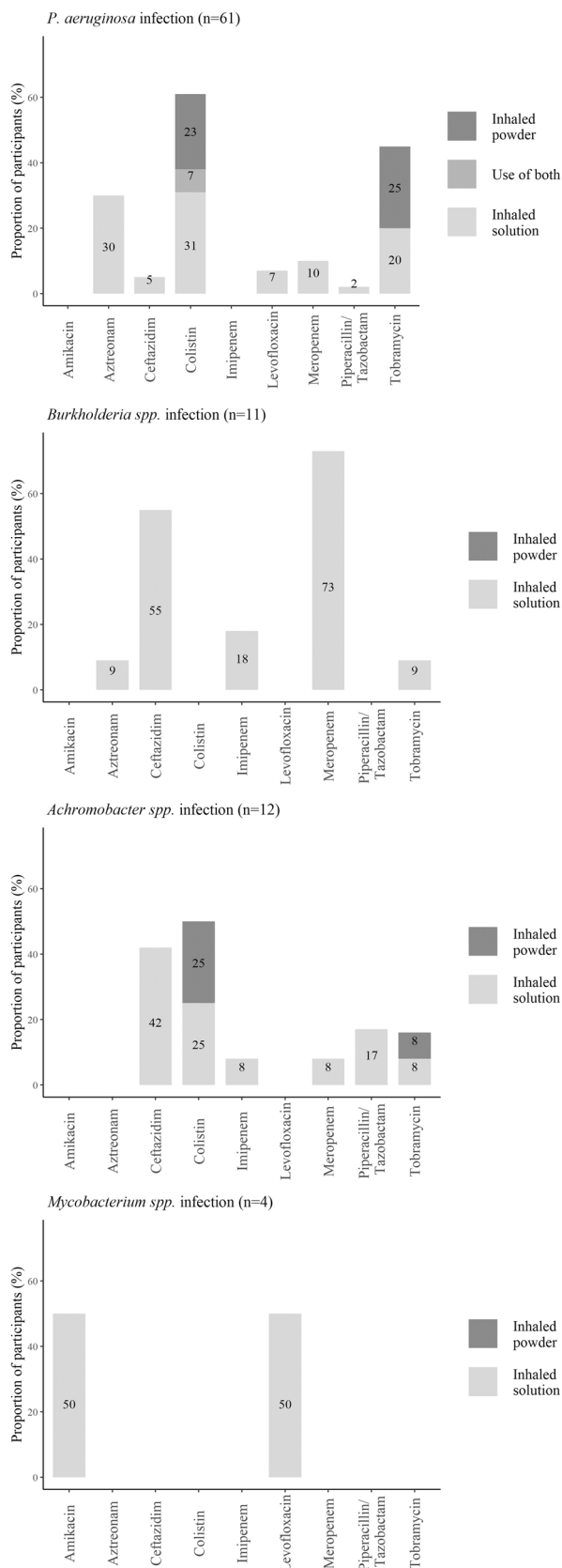[f]Participants were divided to only one of the groups.

intervals were calculated (Table 2). Where appropriate, further statistical tests were applied to investigate the significance of findings, including χ^2 test (Figure 3), two-way analysis of variance test (Figure 3), and independent two-group Mann Whitney *U* test (Supporting Information: Figure 2). To estimate adherence by inhalation device (Figure 3), we stratified participants into "high" or "low" adherence behavior to eliminate bias by general adherence. Stratification was based on adherence to nonantibiotic inhalations (i.e., dornase-alpha), with high adherence defined as "always or almost always" adhering to nonantibiotic inhalations, which all patients should use. Barriers and motivations to adherence were analyzed for all patients with the use of inhaled antibiotics within three months, regardless of infection status (Supporting Information material Figure 3).

3 | RESULTS

3.1 | Participants

Of the 254 CF patients eligible for the study, 157 patients (62%) were approached and 149 (59%) participated (Supporting Information: Figure 1). All demographics are shown in Table 1. Median (IQR) age was 31 (24–41) years and 135 (91%) had severe CF transmembrane regulator (CFTR) mutations (classes I–III). Employment of 15 h or more on a weekly basis was reported by 101 participants (68%). In total, 107 participants (72%) had minimum one pathogenic Gram-negative bacteria and were included in the study group. The participants in the study group were infected

P. aeruginosa infection (n=61)

Burkholderia spp. infection (n=11)

Achromobacter spp. infection (n=12)

Mycobacterium spp. infection (n=4)

with *P. aeruginosa* (*n* = 74), *Burkholderia* spp. (*n* = 15), *Achromobacter* spp. (*n* = 20), or *Mycobacterium* spp. (*n* = 8). Ten participants had coinfection with two of the mentioned bacteria and were counted in both groups. In total, 47 participants had started triple CFTR modulator therapy on the date of inclusion. Of these, 13 started more than three months before inclusion, and the overall median (IQR) treatment time was 35 (28–264.5) days.

3.2 | Inhalation patterns

In the study group, 97 (91%) had used inhaled antibiotics within the past 12 months. The most common regime was continued use of a single inhaled antibiotic, which was reported by 58 (54%) participants. One-third reported to have changed inhaled antibiotics in the previous year, while alternating between multiple different antibiotics
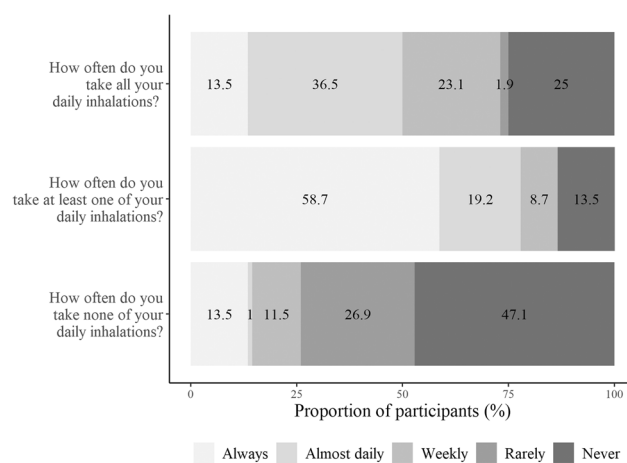

FIGURE 2 Self-reported adherence to inhaled antibiotics used in the last 12 months for patients with cystic fibrosis (*n* = 104). The figure shows the self-estimated adherence to inhaled antibiotics as a percentage of participants reporting a given frequency of use of (upper bar) all daily doses, (middle bar) at least one daily dose, and (lower bar) no doses. Participants who reported no use of inhaled antibiotics were placed in the lowest adherence category (i.e., "Never"). Three participants from the study group with infections eradicated more than three months before study inclusion were excluded from the analysis.

FIGURE 1 Distribution of inhaled antibiotics used in the treatment of different lung infections at the Copenhagen CF Centre among 88 participants with cystic fibrosis. Data are shown as the percentage of participants by infection. Participants with infection and use of any inhaled antibiotic within 12 months before study inclusion are included in the analysis. Nine participants were excluded due to coinfection with two or more of the four bacteria.
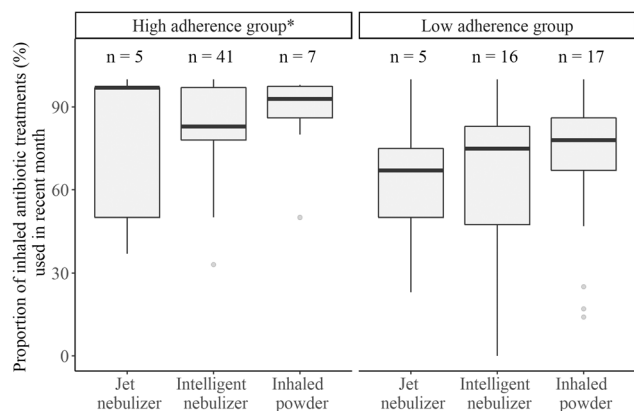
FIGURE 3 Frequency of use of inhaled antibiotics by an inhalation device in recent month among 91 participants with cystic fibrosis stratified by adherence to nonantibiotic inhalations. Box plot with data shown as median (thick) and IQR (lower and upper hinges of box). Analysis includes participants with treatment indication and use of inhaled antibiotics within three months. No difference in frequency of inhaled antibiotic use was found between users of nebulized and powder devices ($p = 0.307$, two-way analysis of variance ANOVA test). Powder devices were significantly more frequent among participants in the low-adherent group ($p = 0.002$, χ^2 test). *High adherence defined as always or almost daily adhering to nonantibiotic inhalation treatment.

was reported by eight (7%) participants. None of the participants inhaled in a regular on/off pattern or inhaled multiple antibiotics simultaneously. Counting all types of inhaled antibiotics ever tried, 74 (69%) had tried three types or more (Table 2).

3.3 | Types of inhaled antibiotics

Among 61 participants with *P. aeruginosa* infection, who had inhaled antibiotics within 12 months, colistin (nebulized/inhaled powder) was the most frequently used ($n = 37$ [61%]), followed by tobramycin (nebulized/inhaled powder; $n = 27$, [45%]) and az-treonam ($n = 18$ [30%]; Figure 1). Other inhaled antibiotics reported by this patient group included levofloxacin, meropenem, piperacillin/tazobactam, and ceftazidime. Off-label antibiotics had been used by 10 participants with *P. aeruginosa* infection (16%), while the number was 17 (25%) when including in the analysis the eight participants with coinfection with *P. aeruginosa* and one of the other three bacteria. A total of 40 participants used inhaled antibiotics off label to treat non-*Pseudomonas* infections: 28 participants used inhaled antibiotics against *Achromobacter* spp., *Burkholderia* spp., or *Mycobacterium* spp., and additionally, among the 42 participants with no local guideline defined indication for inhaled antibiotics, another 12 participants (29%) had used inhaled antibiotics during the previous 12 months (Table 2). This was due either to treatment of infections not usually treated with inhaled antibiotics, that

is, *Staphylococcus aureus* or rare Gram-negative bacteria, chronic infection in transplanted lungs, or poor clinical status.

3.4 | Bacterial susceptibility

In the study group, 30 participants (28%) had used an antibiotic within the last 12 months, despite known decreased susceptibility to the drug. Similarly, 23 participants (21%) were currently using an inhaled antibiotic which their most recent culture was resistant to (Table 2). The median (IQR) perceived health benefit from the use of inhaled antibiotics was 9 (8–10) among participants with bacteria resistant to their current inhaled antibiotic compared to 8 (7–10) among participants with susceptible isolates ($p = .089$) (Supporting Information: Figure 2).

3.5 | Adherence to treatment

Among the 104 participants in the study group with ongoing infection, 52 patients (50%) reported to always or almost always be adherent to all prescribed daily doses, whereas the equivalent number was 81 (78%) for at least one daily dose (Figure 2). Asking about nonadherence instead of adherence did not alter the results. The participants reported to have used 79% (IQR: 50%–94%) of all their prescribed doses in the previous month. Adherence to inhaled antibiotics was consistent across all types of inhalation devices (jet or intelligent nebulizer vs. inhaled powder) when stratified by adherence to nonantibiotic inhalations (high/low) ($p = 0.307$; Figure 3). Inhaled powder devices were used more frequently among participants with lower adherence (45%) compared to participants with higher adherence (13%; $p = 0.002$).

3.6 | Motivations and barriers

Variation in motivations and barriers stratified by age group is shown in Supporting Information: Figure 3. Motivations for use of inhaled antibiotics were mostly related to health outcomes, with symptom reduction and maintenance of good health being reported most frequently (51% and 41%, respectively). The most common barriers to adherence were "logistical or practical challenges" (51%), followed by "lack of personal resources" (37%), "forgetting" (27%), and "deviance from routine" (20%). Side effects as a reason for missed inhalations were reported by 4%, and more often than skipping inhalations, side effects resulted in a change of inhaled antibiotic (data not shown). Skipping inhalations due to lack of effect was reported by 3%.

4 | DISCUSSION

Our study aimed at characterizing the use of inhaled antibiotics in the Copenhagen CF population, focusing on parameters of tailored prescription of inhaled antibiotics and adherence to treatment. Use of

inhaled antibiotics was reported by the vast majority of participants with an indication for treatment (study group) and change of antibiotic type as well as the use of off-label antibiotics was common. Self-estimated adherence to one daily inhalation was high, and was motivated predominantly by health-related factors, whereas barriers to adherence were primarily related to logistical challenges.

Our findings in the Copenhagen CF population, where 91% of patients with relevant infections reported use of inhaled antibiotics within the last 12 months, are similar to results from the UK[19] and the USA,[20] probably representing the realistic upper limit. Regular on/off-patterns were not reported by any of our participants despite widespread use of tobramycin and aztreonam. While international guidelines refer to studies of 28-day cycle treatment with these antibiotics,[1,2] continuous treatment is our local policy.[5] Our results indicate that this is accepted by the patients, with no reports of regular inhalation pauses.

The use of off-label prescriptions was widely observed in our population. While the three inhaled antibiotics most used in the treatment of *P. aeruginosa* (colistin, tobramycin, and aztreonam) are recommended by European guidelines,[1] a range of off-label inhaled antibiotics, including meropenem and piperacillin/tazobactam, were used in the treatment of 25% of participants with *Pseudomonas*-infection. Additionally, due to lack of inhaled antibiotics approved for treatment of non-*Pseudomonas* infections, a large group of patients with other bacteria was prescribed inhaled antibiotics off-label. Change of antibiotics was also frequent, and overall, 69% of participants in the study group had tried at least three types of inhaled antibiotics in their lives. These findings reflect a demand for a wider selection of different antibiotics, developed for inhalation and easy to manage. More antibiotic options may also help improve long-term efficacy and adherence according to Döring et al.[1]

Another issue with the long-term use of antibiotics is development of resistance, but standard susceptibility testing correlates poorly with clinical effects.[21] In our study group, 28% had used inhaled antibiotics to which their bacteria had previously shown resistance. This reflects a practice where subjective effect and preference may outweigh in vitro resistance when choosing a treatment strategy, a prioritization which is not unique to our setting.[22] Surprisingly, our results showed higher perceived health benefits among participants inhaling antibiotics against resistant bacteria. This might be explained by differences in age and lung function, but moreover, may reflect an effect of inhaled antibiotics on slower growing, susceptible subcultures or alternate pathogens, or even an anti-inflammatory component.[23] It may be due to the achievement of high local concentrations of antibiotics in the airways.[23] These factors, while beneficial for the patient, are independent of the results of standart susceptibility testing. Indeed, while susceptibility analyses are adequate when identifying antibiotics to eradicate an infection, antibiotics for suppressive treatment in CF have a different purpose, since the infection cannot be eradicated. Thus, while the results may sanction our current prescription practice, they should be interpreted carefully due to the many confounding elements.

In the study group, 78% of the participants managed to use their inhalations at least once daily almost every day. Less encouraging, only 50% reported using all their prescribed inhalations this frequently. This confirms trends described in earlier studies,[10,24] and may suggest that for a group of patients, inhaling twice daily is challenging to manage. Standardized use of dornase-alpha from early childhood may accustom all patients to once-daily inhalations, whereas more frequent inhalations require new habits. The recent approval of a once-daily inhaled antibiotic[25] is a promising development, although further studies in patients with CF are needed. Adherence was not affected by the inhalation device as seen in other studies;[7,8] however, this could be due to a bias in who receives a prescription of inhaled powder. Consistently, inhaled powder was used significantly more often by participants with low adherence behavior compared to those with high adherence. This may be caused by patient preference but could also reflect that these patients are more readily proposed a switch to an easier device, although highly adherent patients might also benefit from inhaled powder devices.

Motivations for use of inhaled antibiotics were largely health related. Maintenance of health was almost as frequently reported as immediate symptom reduction, suggesting that many patients understand the long-term importance of adhering to treatment. Frequently reported barriers to adherence included forgetting and lacking the personal resources, that is, fatigue or lack of mental energy, consistent with previous reports from CF populations.[3,26] Most perceived barriers, however, could be linked to the circumstances regarding inhalation therapy, such as logistical challenges or deviance from routines, like going out at night. In contrast, very few participants reported side effects or lack of effect as the reason for skipped inhalations. This suggests that patients indeed wish to adhere to treatment, but find that it conflicts with their efforts to live a normal life, a paradox previously reported from our cohort.[27] Finally, the absence of reports of negative consequences of side effects and experience of no effect in our study emphasize why it is helpful to personalize treatment.

4.1 | Strengths and limitations

Our rate of participation was high, likely since the study consisted of a single interview. Recruitment took place sequentially on random visit days to minimize selection bias. The simple study design allowed participation regardless of the use of inhaled antibiotics, inhalation device, antibiotic type, or infection.

A limitation of the study was the use of self-reporting, as this method has been shown to systematically overestimate adherence when compared to objective measures.[28,29] Specifically, in regard to our conclusions, participants may be more ready to admit partial nonadherence than complete nonadherence. Additionally, we estimated adherence over a long period, which may increase this tendency. However, for the scope of this study it was deemed appropriate. To achieve a short, accessible questionnaire, all

nonantibiotic inhalations were pooled, making it difficult to uniformly estimate the general adherence (e.g., only dornase alfa) for the adherence by device analysis. Study inclusion started just before the rollout of triple CFTR modulator therapy; however, 47 participants had already started treatment upon inclusion. Although continued antibiotic inhalations were recommended, five participants reported consequent major changes in adherence behavior (not part of the questionnaire). Based on this limited data, triple therapy is likely to change the outcome of our study if repeated in the future, but presently will not have substantially affected our data, since our main outcomes are based on data from the past year and the overall treatment time before inclusion in our study was much shorter than this.

5 | CONCLUSION

Among adolescents and adults living with CF, inhaled antibiotics were used by the vast majority of patients with relevant infections, indicating successful implementation of local and European guidelines. Most participants followed the centre standard of continuous inhalation of the same antibiotic. Change of antibiotics and use of off-label antibiotics were frequent, reflecting a practice of tailored prescription toward the cultured microorganisms and patient needs. However, adherence to minimum one daily inhalation was more frequent compared to multiple daily inhalations, suggesting room for improvement and warranting investigation into non-inferiority of once versus twice daily inhalations. Expanding the principle of personalized treatment to include more types of antibiotics and simple delivery methods might increase adherence to all doses.

AUTHOR CONTRIBUTIONS

Rikke Møller: formal analysis (lead); investigation (lead); visualization (equal); writing—original draft (lead). **Bibi Uhre Nielsen**: formal analysis (equal); supervision (equal); visualization (equal); writing— review & editing (lead). **Daniel Faurholt-Jepsen**: formal analysis (equal); methodology (equal); writing—review & editing (equal). **Terese L. Katzenstein**: conceptualization (equal); methodology (equal); writing—review & editing (equal). **Marianne Skov**: conceptualization (equal); writing—review & editing (equal). **Lue Phillipsen**: Resources (equal); writing—review & editing (equal). **Tacjana Pressler**: conceptualization (equal); methodology (equal), writing—review & editing (equal). **Helle Krogh Johansen**: conceptualization (equal); supervision (equal); writing— review & editing (equal). **Tavs Qvist**: conceptualization (equal); funding acquisition (equal); methodology (equal); supervision (equal); writing—review & editing (lead).

CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.