CANADIAN CONSENSUS STATEMENT ON AEROSOLIZED ANTIBIOTIC USE IN CYSTIC FIBROSIS

CYSTIC FIBROSIS CANADA
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Cystic Fibrosis Canada
Fibrose kystique Canada

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OUTLINE

DEFINITIONS

Pa – *Pseudomonas aeruginosa*

MRSA – methicillin-resistant *Staphylococcus aureus*

Bcc – *Burkholderia cepacia* complex

NIT – nebulized intravenous tobramycin

TIS – tobramycin inhalation solution (TOBI®)

TIP – tobramycin inhalation powder (TOBI® Podhaler)

AIS – aztreonam inhalation solution

LIS – levofloxacin inhalation solution

ALIS – amikacin liposomal inhalation suspension

FTI – fosfomycin/tobramycin inhalation solution

SECTION I. INTRODUCTION

In 1999, the Canadian Cystic Fibrosis Foundation (CCFF) drafted its first Canadian consensus statement on aerosolized antibiotics. At that time, the intravenous preparation of tobramycin and colistin were the principal preparations in use for aerosolization, with preservative-free high-dose tobramycin (TOBI®) just entering the Canadian market. Since then, TOBI® has become one of the most widely used aerosolized products, especially for early or new-onset *Pseudomonas aeruginosa* (Pa) eradication. In addition, other products, such as aztreonam, amikacin, colistin, levofloxacin and vancomycin are also used in the care of individuals with cystic fibrosis (CF) affected with infections caused by Pa, *Burkholderia cepacia* complex (Bcc) as well as methicillin-resistant *Staphylococcus aureus* (MRSA).

In light of recent advances, a subcommittee of CF Canada, comprised of Healthcare Advisory Council and Subcommittee members, have joined efforts to update the most recent 2006 statement on the use of inhaled antibiotics in CF. Building upon this past statement, the mandate of this task force was to: 1) review the available data on inhaled antibiotics in CF and 2) develop an updated guide for Canadian CF clinics.

In this document, the current evidence is summarized and recommendations based on a standard rating system (Appendix I) were elaborated. Appendix II and III discuss compressors and aerosolized antibiotics respectively, and the references at the end of the document are the source of material utilized in the development of this statement. It is not intended to be all-inclusive, but rather as support for the comments made in this statement.

SECTION II. RATIONALE FOR THE USE AND CLINICAL EFFICACY OF INHALED ANTIBIOTICS FOR TREATMENT OF CF AIRWAY INFECTIONS

1. *PSEUDOMONAS AERUGINOSA* INFECTION

Chronic airway infection caused by Pa remains one of the main causes of accelerated mortality in individuals with CF. Pa is known to produce toxins and virulence factors which can cause airway damage (1). In particular, neutrophilic airway inflammation stimulated by the production of Interleukin-8 contributes to the development of bronchiectasis (2). In addition, chronic phenotypes of Pa, such as the conversion from non-mucoid to mucoid status, are associated with poorer clinical outcomes (3).

In order to achieve effective and high-concentration delivery of antimicrobials to the airway while minimizing systemic exposure, the use of inhaled antibiotics has become widely prevalent in CF care (4). Although tobramycin and colistin have been more commonly used, other antibiotics such as aztreonam and levofloxacin are increasingly used as anti-pseudomonal therapies. Tobramycin was initially approved in 1997 as a solution for inhalation, and then more recently as a dry powder inhaler in 2013.

The three main goals of inhaled antibiotic therapy are: a) early eradication of first time or new-onset Pa infection, b) Pa suppression therapy in patients with chronic Pa infection, and c) treatment of acute pulmonary exacerbations.

a) Early eradication

A number of studies have investigated Pa eradication before infection becomes established and permanent in the CF airways. Most published approaches have used, or included, inhaled antibiotics. Initially, many studies that were published tended to be small, and were often non-blinded. For example, Littlewood et al. administered colistin 0.5 million units twice daily to 7 children with CF after first isolation of Pa and found that the frequency of positive Pa cultures was lower in the following 3-13 months (5). Valerius and coworkers reported using a 3-week regimen of inhaled colistin 1 million units twice daily and ciprofloxacin whenever Pa was isolated in the sputum in a small, non-blinded study. Over 27 months, 58% of untreated patients developed chronic Pa infection (defined using sputum cultures and/or precipitating anti-Pa antibodies) versus 14% of the treated patients ($p<0.05$) (6). In another study, the same group used inhaled colistin 1-2 million units twice daily and oral ciprofloxacin, initially for 3 weeks upon first sputum isolation of Pa. Treatment was given for 3 months upon the third isolation of Pa within a 6- month period. Over the next 30 months, 15% of subjects developed chronic Pa infection (defined as in the study by Valerius and coworkers), compared to 44% of historical controls ($p < 0.005$). Treatment was also reported to significantly reduce anti- Pa precipitating antibodies, the proportion of sputum samples positive for PA, and the decline in forced expiratory volume in 1 second (FEV_1) (13). Wiesemann et al. used nebulized intravenous tobramycin (NIT) 80 mg twice daily or placebo, inhaled by jet nebulizer for 12 months in a randomized, double-blind trial in a very small group of children with CF recently infected with Pa who had negative anti-Pa antibodies and no positive cultures for Pa in the preceding 12 months. Cultures became negative in the treated group and pulmonary function was similar in both groups. However, anti-Pa antibody titers were lower in the treated group (7).

Gibson and coworkers conducted the first randomized double-blind placebo-controlled multicentre trial to test the hypothesis that 300 mg of TIS twice daily for 28 days would be safe, and decrease Pa density from lower airways of young CF children (aged 6 months to 6 years). The trial was stopped early because a significant treatment effect was observed. All randomized patients had Pa positive baseline bronchoalveolar lavage cultures, and on day 28 of the trial, no Pa was detected in 8 of 8 active group patients, versus 1 of 13 in the placebo group. However, the study did not look at other outcome measures, and the duration of the study was very short (8).

In an open-label, randomised multicentre study, Ratjen et al. described short- and long-term efficacy and safety of TIS 300 mg/5 ml twice daily for 28 and 56 days in the treatment of early onset Pa infection in patients aged ≥6 months with CF (9). Early infection was defined as a new detection of Pa in a respiratory culture after negative cultures for at least 1 year (if at least four documented negative cultures were available) or up to 2 years with four documented negative cultures in this time period (in the absence of anti-pseudomonal treatment). All patients received TIS twice daily for 28 days administered via PARI LC PLUS jet nebulizer. Randomisation occurred at day 28. Patients were excluded from randomisation if Pa-specific antibody titres taken at day 1 were elevated (≥1000 units). Eligible patients at day 28 were randomised 1:1 to either stop study medication (28-day group) or to receive an additional 28 days of treatment (56-day group). The median time to recurrence of Pa was similar between the two groups. In total, 93% and 92% of the patients were free of Pa infection 1 month after the end of treatment and 66% and 69% remained free at the final visit in the 28-day and 56-day groups, respectively. The authors concluded that treatment with TIS for 28 days was a safe and effective duration of antibiotic eradication therapy for patients with early or new-onset Pa infection. Of note, a recent double-blind, placebo-controlled trial of children with CF aged <7 years further demonstrated the efficacy of 28-day course of TIS for Pa eradication in young children, whom were often underrepresented in previous trials. On day 29, 84.6% patients in the TIS versus 24.0% in the placebo group were Pa-free ($p \leq 0.01$) (10).

Treggiari et al. further defined the evidence for early eradication therapy in children by conducting a multicentre, open-label randomized controlled trial comparing the efficacy and safety of 4 anti-pseudomonal treatment regimens in 304 children with CF (11). Pa infection was defined as a documented respiratory tract culture positive for Pa within the six months prior to randomization – with new isolation of Pa defined as the first ever in the lifetime documented positive respiratory tract culture or as a positive culture after at least two-year absence of Pa growth on culture. The four antibiotic eradication regimens that were compared included: a) TIS combined with oral ciprofloxacin every 3 months, b) scheduled TIS combined with oral placebo every 3 months, c) TIS combined with oral ciprofloxacin only when quarterly respiratory cultures were found to be positive for Pa and d) TIS combined with oral placebo only when quarterly respiratory cultures were found to be positive for Pa. The primary endpoint was time to the first pulmonary exacerbation requiring intravenous antibiotics or hospital admission during the study period. Overall, there were no differences in the rate of exacerbation or prevalence of Pa positivity. The authors stressed that adding ciprofloxacin to antibiotic eradication therapy for early Pa infection led to no benefits.

In 2018, the OPTIMIZE trial (12) evaluated the effect of treatment with TIS with and without azithromycin in people with CF with new-onset or first ever infection with Pa. Participants were randomized to receive oral azithromycin (10 mg/kg up to a maximum of 500 mg per dose) or placebo three times a week for 18 months. All participants received TIS therapy (300mg twice daily delivered by inhalation using the PARI LC PLUS™ nebulizer) during the first treatment quarter, consisting of a 28-day course of TIS therapy with a second 28-

day course for those participants who remained Pa positive at 21 days. Risk of pulmonary exacerbation (primary endpoint) was reduced by 44% in participants receiving oral azithromycin in addition to TIS therapy when compared with placebo (p=0.046). However, no significant differences were seen in terms of microbiological eradication of Pa.

Based on the efficacy of aztreonam inhalation solution (AIS) for chronic Pa infection, an open-label, multicentre study was done to assess the use of AIS for early eradication (13). This trial included 105 paediatric patients (including young children age 3 months and above) who had newly detected Pa growth in respiratory tract culture (within 30 days of screening) defined as either the first lifetime positive or positive after at least 2 years of negative cultures (with at least 2 negative cultures per year). The primary outcome was the proportion of patients with cultures negative for Pa at all visits throughout the 24-week follow-up period. Overall, 89.1% of patients who completed treatment with aztreonam (n=101) cleared Pa at the end of 28 days of treatment and 75% remained Pa culture negative up to 4 weeks after the end of treatment. The authors concluded that inhaled aztreonam was a safe and effective therapeutic option for children with early Pa infection.

b) Chronic suppression

Nebulized tobramycin has also been used to suppress Pa activity and to slow the decline in lung function in CF patients.

In a small, non-blinded study, MacLusky and coworkers showed that NIT 80 mg three times daily by jet nebulizer significantly reduced the rate of decline of forced expiratory volume in 1 second (FEV_1) over a 30 month period (annual decline 0.7 versus –7.1 % predicted, $p < 0.01$) (14). Similarly, in another small, non-controlled study, Steinkamp and coworkers, showed that NIT 80 mg twice daily by jet nebulizer for 1 year led to a slowing of the decline in Forced Vital Capacity (FVC) and an improvement in nutritional status (15). In a larger, randomized, placebo-controlled study, Ramsey et al. used a high dose of NIT, 200 mg three times daily delivered by ultrasonic nebulizer for 1-2 months (16). This dose was chosen on the basis of earlier work showing this approach delivered highly effective concentrations of NIT into CF sputum (4). NIT was associated with an overall improvement in FEV_1 of 4.3% (p=0.002). There were also significant reductions in sputum Pa density, peripheral white blood cell counts, and the need for oral or intravenous (IV) antibiotic therapy (16).

While initial studies used NIT, most recent studies have used a commercially available preservative-free preparation, TIS (developed specifically for nebulization therapy in CF patients). In a follow up large, randomized, placebo-controlled study, Ramsey et al. used TIS 300 mg twice daily or placebo by jet nebulizer for 3 1-month periods, each separated by a 1-month period off therapy. At week 20, those receiving TIS had a 10% increase in FEV_1, while FEV_1 declined by 2% in the placebo group ($p < 0.001$). There were also significant reductions in sputum Pa density, hospitalization, and need for IV anti-pseudomonal antibiotics (17). Moss reported on studies performed with the same dose of TIS, administered for 72 weeks in an open label extension of the randomized, double-blind trial in adolescents 13-17 years of age. FEV_1 improved by 14.3% with TIS treatment, compared to 1.8% with those originally randomized to placebo, at the end of 92 weeks of observation. Hospitalizations were not affected by treatment, but the body mass index improved significantly in placebo patients who crossed over to TIS (week 24 to week 48) (18). In a non-blinded randomized study of alternating months of TIS administered to children with CF 6-10 years of age with an FEV_1 of at least 70% predicted, hospitalization and use of any oral antibiotics were significantly reduced, although hospitalization rates were again quite high, with a 26% rate of hospitalization in the placebo group. There were no significant changes in FEV_1 (19).

In 2013, an open-label phase III trial involving over 553 patients with CF aged ≥6 years showed comparable effectiveness of TIP compared to TIS, with similar FEV_1 increases and mean reduction in sputum Pa density. Administration time was significantly less for TIP (mean: 5.6 versus 19.7min, p<0.0001) (20). Treatment satisfaction, convenience, and global satisfaction was significantly higher for TIP (20). However, the rate of cough suspected to be drug-related was higher in TIP-treated patients (TIP: 25.3%; TIS: 4.3%), as was the overall discontinuation rate (TIP: 26.9%; TIS: 18.2%) (20). Another trial (EVOLVE (21)) evaluated the efficacy and safety of TIP in a randomized, double blind placebo-controlled study involving children and young adults 6 to 21 years of age. Patients treated with tobramycin inhalation powder had significantly improved FEV_1 compared to those treated with placebo at Day 28 (difference 13.3, 95% CI: 5.31-21.28; P = 0.0016); these changes were maintained over the next cycle of therapy. TIP treatment also reduced sputum Pa density, respiratory-related hospitalization and other anti-pseudomonal antibiotic use compared to placebo use. The most common adverse event was cough, which was found more commonly in patients receiving the placebo than in patients treated with TIP (26.5% versus 13.0%, respectively). Overall, the authors concluded that TIP was a safe and effective treatment option to decrease the treatment burden of Pa infections in individuals with CF.

A randomized, double-blind, placebo-controlled study in 211 individuals with CF (aged 6 years or older) was conducted to evaluate the safety and efficacy of AIS (75 mg BID or TID) for 28 days in controlling Pa infection in patients with CF who had 3 or more courses of TIS for chronic Pa within the previous year (22). The primary efficacy endpoint was time to additional inhaled or intravenous anti-pseudomonal antibiotics, with secondary endpoints such as changes in respiratory symptoms, FEV_1, and sputum Pa density. Aztreonam treatment increased median time to need for additional anti-pseudomonal antibiotics for symptoms of pulmonary exacerbation by 21 days, compared with placebo (p≤0.01). Aztreonam also improved mean respiratory scores (p=0.02), FEV_1 (6.3%, p≤0.01), and decreased sputum Pa density (-0.66 log (10) cfu/g, p≤0.01) compared with placebo. Overall, AIS was felt to be safe and effective in patients with CF using frequent TIS therapy. Similarly, in a randomized, double-blind, placebo-controlled trial in patients with CF and chronic Pa infection who had no recent use of anti-pseudomonal antibiotics or azithromycin oral therapy, AIS (75 mg TID) was found to improve mean respiratory score, FEV_1 and sputum Pa density compared with placebo (23). In addition, a recent double-blind trial published by Flume et al. (24) compared 3 cycles of 28-days AIS (75 mg TID) or placebo, alternating with 28-days open-label TIS in 90 randomized subjects. The alternating combination of aztreonam with TIS reduced exacerbation rates by 25.7% (p=0.25); rates of admission to hospital for respiratory symptoms were reduced by 35.8% compared to placebo combination (p=0.14). Overall, the authors concluded that the alternating combination of aztreonam and TIS was safe, well tolerated and possibly provided additional clinical benefits compared to intermittent TIS alone in chronic Pa infection. Of note, this study was underpowered due to limited study enrollment.

Combination fosfomycin/tobramycin for inhalation (FTI) was studied in a double blind, placebo-controlled multicentre study to assess safety and efficacy (25). Varying doses of the combination were administered (80/20 mg or 160/40 mg) twice daily for 28 days and compared to volume-matched placebo in adult patients with chronic Pa airway infection, after a 28-day, open-label, run-in course of inhaled aztreonam. Overall, 119 patients were randomized. Relative improvements in FEV_1 percent predicted achieved by the inhaled aztreonam run-in were maintained in FTI groups compared with placebo (160/ 40 mg versus placebo: 6.2% treatment difference favoring FTI, p= 0.002; 80/20 mg versus placebo: 7.5% treatment difference favoring FTI, P<0.001). Furthermore, the treatment effect on mean Pa sputum density was statistically significant.

Inhaled colistin has also been used as a chronic suppressive treatment. Jensen and coworkers administered colistin 1 million IU (or placebo) twice daily for 3 months to a small group of CF patients who had just completed a course of intravenous therapy, in a randomized double-blind fashion. There was less of a decrease in FVC with colistin therapy (7% drop versus 18% drop, $p<0.05$), clinical scores were significantly higher, and fewer patients dropped out of the study compared to no colistin treatment. Pa was not eradicated from the sputum of any patient (26). A European randomized open-label clinical trial involving 115 patients with chronic Pa infection (aged 6 years and older) compared TIS versus colistin sulphomethate sodium (80 mg) inhaled twice daily for four weeks (27). The primary endpoint was relative change in lung function from baseline, with a secondary outcome of Pa sputum density. The TIS-treatment group had a significantly greater improvement in FEV_1 percent predicted (6.7% versus 0.37%, $p\leq0.01$) compared to the colistin group. Furthermore, in the intent to treat analysis at week 4, the mean decrease in Pa density was greater in TIS-treated patients than in colistin-treated patients ($p\leq0.01$). The authors concluded that both nebulized antibiotics had acceptable safety profiles, but that TIS may be the preferred agent when choosing an inhaled antimicrobial regimen for chronic Pa infection, compared to colistin. Recently, in a 24-week randomized non-blinded trial of 380 patients with CF (aged ≥6 years) and chronic Pa infection, the efficacy of dry powder colistin for inhalation (one capsule containing colistimethate sodium 1 662 500 IU, twice daily) versus TIS was evaluated. In this study, colistin was found to be non-inferior to TIS and well tolerated (28).

Inhaled levofloxacin is another treatment option for chronic Pa infection in individuals with CF. A multinational, randomized double-blinded placebo-controlled study showed no difference in time to next exacerbation between individuals with CF (aged 12 years or older) with chronic Pa infection treated with levofloxacin inhaled solution (LIS; 240 mg BID) and those treated with placebo (29). However, a significant improvement in FEV_1 was observed in the LIS group. Of note, another multi-national, randomized non-inferiority clinical trial compared LIS (240 mg BID) to TIS (300 mg BID) in individuals 12 years and older with CF and chronic Pa infection (30). The main outcome was relative change in FEV_1 at day 28. Non-inferiority was demonstrated, (1.86% predicted mean FEV_1 difference [95% CI -0.66 to 4.39%]) and LIS was overall well tolerated.

Liposomal formulations of amikacin (Arikayce™) for inhalation (ALIS) have been studied in CF patients with chronic Pa. In 2013, the safety and efficacy of 28 days of once-daily ALIS in CF patients chronically infected with Pa were evaluated in a double-blind, placebo-controlled study. Overall, 105 subjects were randomised to once-daily ALIS (70, 140, 280 and 560 mg; n=7, 5, 21 and 36 subjects) or placebo (n=36) for 28 days. The relative change in FEV_1 was higher in the 560 mg dose group at day 28 ($p=0.033$) and at day 56 ($p=0.003$) compared to placebo. Sputum Pa density decreased >1 log in the 560 mg group versus placebo (days 14, 28 and 35; $p=0.021$). The Respiratory Domain of the CFQ-R increased by the Minimal Clinically Important Difference (MCID) in 67% of ALIS subjects (560 mg) versus 36% of placebo ($p=0.006$), and correlated with FEV_1 improvements at days 14, 28 and 42 ($p<0.05$). In addition, adverse events did not significantly differ between ALIS and placebo subjects (31). In 2019, a randomized open-label, active-controlled study was published to describe the efficacy of ALIS (590 mg once daily) versus TIS (300 mg BID). This large study included 302 patients with CF (aged 6 years or more) with chronic Pa infection, followed at 70 sites in Europe and Canada. The primary endpoint was the change in FEV_1 from baseline to day 168 of treatment. The authors concluded that intermittent inhaled amikacin therapy – with the benefit of being administered once daily – was non-inferior to twice-daily TIS in terms of maintaining lung function in patients with chronic Pa infection (32).

Although ciprofloxacin dry powder has shown some promising effects to reduce pulmonary exacerbations in non-CF related bronchiectasis patients (33, 34), an adequately powered double-blind, placebo-controlled study in individuals with CF (aged 12 years and older) and chronic Pa infection failed to meet its primary end point of change in FEV_1 from baseline to the end of inhaled treatment at 29 days (using 32.5 mg or 48.75 mg versus placebo twice daily for 28 days) (35). In this study, an antimicrobial effect with a reduction of approximately 1.5 log CFU/g at day 14 was not sustained at day 29 at which point the difference was not significant compared to placebo. The drug was well tolerated and the authors concluded that further studies were needed to determine the full potential of ciprofloxacin dry powder in CF.

c) Treatment of acute pulmonary exacerbation

In the published literature, two previous trials have assessed the efficacy of inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics alone for the treatment of pulmonary exacerbations. Stephens and coworkers (36) reported a small, non-blinded study comparing intravenous antibiotic therapy for acute pulmonary exacerbations in children with CF to intravenous therapy plus NIT 80 mg three times daily by jet nebulizer. While sputum Pa colony counts declined with NIT, there were no differences between the groups in pulmonary function, arterial oxygen pressure, or Shwachman score (a marker of CF disease severity (37)). In addition, Schaad and coworkers allocated patients admitted with a pulmonary exacerbation to intravenous antibiotic therapy alone, or combined with inhaled amikacin 100 mg twice daily by jet nebulizer. Pulmonary function, clinical status, and hematological evidence of inflammation were not affected by inhaled antibiotic therapy. Pa was eradicated in the sputum significantly more often in subjects treated with the addition of inhaled amikacin, but most patients were sputum culture positive again within 4-6 weeks (38).

2. METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) INFECTION

MRSA infection has been associated with poor clinical outcomes in individuals with CF, including accelerated lung function decline (39, 40) and increased risk of earlier death (41). Therapeutic options to treat MRSA are limited and usually include vancomycin as the backbone of intravenous therapy, and/or oral agents such as trimethoprim-sulfamethoxazole (TMP/SMX), clindamycin or linezolid. The STAR-Too trial previously assessed the effectiveness of antibiotic eradication therapy for MRSA infection; patients were randomized to either oral and topical combination therapy plus environmental decontamination, or to an observational control group. The intervention seemed to significantly reduce the number of individuals with positive respiratory tract cultures for MRSA at day 28 (42). However, there are no current published trials on the use of inhaled antibiotics for initial MRSA eradication.

The Persistent MRSA Eradication Protocol (PMEP) was a double blind, randomized, placebo-controlled study investigating a comprehensive 28-day treatment regimen with or without inhaled vancomycin for eradication of persistent MRSA infection. All participants received oral antibiotics, topical decontamination, and environmental cleaning and were randomized to receive either inhaled vancomycin 250 mg twice daily or inhaled placebo. The primary outcome was the difference in MRSA eradication rates one month after completion of the treatment protocol. Overall, 29 participants were randomized. There was no difference in the primary outcome: 2/10 (20%) of subjects in the intervention group and 3/15 (20%) in the placebo group had a MRSA negative sputum culture one month after treatment. There were no statistically significant differences in the rates of MRSA eradication at the end of treatment or three months after treatment completion. The authors concluded that the use of a single course of inhaled vancomycin might not lead to higher rates of MRSA eradication in individuals with CF (43).

A current phase III trial is currently underway, assessing the effectiveness of inhaled vancomycin powder in adults and children 6 years of age and older with CF who are culture positive for MRSA (44). The primary outcome will be the mean absolute change from baseline in FEV_1 percent predicted; analyzed sequentially at Week 4 (end of Cycle 1), Week 12 (end of Cycle 2), and at Week 20 (end of Cycle 3). Secondary outcomes will include time to first pulmonary exacerbation requiring use of another antibiotic (oral, intravenous and/or inhaled), as well as frequency of pulmonary exacerbations and symptom scores.

3. *BURKHOLDERIA CEPACIA* COMPLEX INFECTION

Historically, individuals with Bcc infection have mostly been excluded from clinical trials assessing efficacy and safety of inhaled antibiotics. However, some recent trials have been conducted to assess the efficacy of inhaled antibiotics for Bcc infection in individuals with CF.

In 2014, a randomized, double blind, placebo-controlled, 24-week trial of continuous aztreonam inhaled solution (AIS) versus placebo was performed in 101 individuals 6 years or older with CF and chronic Bcc infection. Tullis and coworkers concluded that AIS did not significantly improve lung function in individuals with CF who had chronic Bcc infection. The number of respiratory exacerbations requiring systemic antibiotics and of hospitalizations was not significantly improved in patients who received AIS (45). Furthermore, a pilot open-label clinical trial of TIP delivered via Podhaler twice daily for 29 days in both adults and children with CF who had chronic Bcc infection was conducted in 2 CF centres of Toronto, Canada (46). In total, 10 subjects were treated including 4 children. Bcc density decreased by a mean of 1.4 log (CFU/mL log10) from day 0 to day 28 of TIP treatment (p=0.01). The mean relative increase in FEV_1 was 4.6% (median 2.4%), which was not statistically significant.

SECTION SUMMARY

In summary, much of the evidence published regarding the use of inhaled antibiotics is focused on treatment of Pa infections in its various stages. Several antibiotics, including NIT, TIS, aztreonam, colistin and levofloxacin have showed efficacy and safety in treating Pa infection. Therapeutic options are much more limited for MRSA, although ongoing studies may provide helpful findings. Future studies are needed to determine which inhaled formulations may be used for treatment of Bcc infections in CF.

SECTION III. BACTERIAL RESISTANCE TO AEROSOLIZED ANTIBIOTICS

One of the greatest concerns surrounding the use of antibiotics is the emergence of bacterial antimicrobial resistance. The relationship between antimicrobial resistance and efficacy of inhaled antibiotics in CF is discussed below.

1. MECHANISMS OF RESISTANCE

In CF, resistance to antimicrobial agents is a consequence of frequent and often prolonged exposure to antibiotics. There are several mechanisms of resistance, which include acquisition of an enzyme that modifies an antibiotic rendering it inactive (e.g., ß-lactamase or aminoglycoside modifying enzyme), mutations in the target site (e.g., mutations in ribosomal subunits for aminoglycosides), or efflux of the agent from the bacterial cell via multidrug-transporters. A strain may express multiple resistance mechanisms often working together synergistically. Surveys of aminoglycoside resistant strains from patients with CF have demonstrated that the majority do not possess known aminoglycoside modifying enzymes (47), but appear to be "impermeable" presumably due to recently described efflux pumps (48). In contrast, aminoglycoside resistant strains from non-CF patients harbor aminoglycoside-modifying enzymes.

In addition, bacteria growing in a biofilm are generally more resistant to antibiotics than bacteria growing in planktonic state (49). Multiple mechanisms of biofilm resistance have been proposed (50) including slow growth due to lack of nutrients, relatively anaerobic environment particularly at the biofilm base, drug diffusion barriers, and lack of expression of the antibiotic target site. In fact, planktonic antimicrobial susceptibility testing does not provide meaningful resistance data for biofilm growing bacteria. Thus, antibiotic resistance, often multidrug-resistance, is expected in patients with CF as a result of selective pressure exerted by antimicrobial therapy, particularly as a high density of microbes is exposed to sub-inhibitory concentrations of drug.

2. ESTABLISHING THE MIC FOR ANTIBIOTICS

Susceptibility testing performed in clinical microbiology laboratories are relevant for antibiotics delivered by the parenteral route. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of an agent that will inhibit the growth of a bacterial isolate (51). The MIC may be influenced by numerous factors including: the size of the bacterial inoculum, the composition of the growth media, the duration and temperature of the incubation, and the presence of resistant sub-populations.

Breakpoints are the interpretive criteria of MIC values that correspond to the categories of susceptible, intermediate, and resistant. The precise cut-off values vary by antimicrobial agent. For example, the breakpoints of *Pseudomonas aeruginosa* for tobramycin are presented in **Table 1** (52):

Table 1.

TOBRAMYCIN BREAKPOINTS	INTERPRETATION BY ANTIBIOTIC DISKS	VALUE BY BROTH MICRODILUTION
Susceptible	S	≤ 4 µg/ml
Intermediate	I	8 µg/ml
Resistant	R	≥ 16 µg/ml

3. LACK OF RELEVANCE OF PARENTERAL BREAKPOINTS FOR AEROSOLIZED ANTIBIOTICS

Conventional breakpoints established for intravenous or oral antibiotics utilizing the above principles are unlikely to be useful for aerosolized antibiotics as much higher concentrations of drug are delivered by this route. At present there are no breakpoints that correspond to susceptible, intermediate, or resistance to aerosolized antibiotics. Potential considerations in the determination of breakpoints for conventional parenteral antibiotics and aerosolized antibiotics are shown in **Table 2.**

Table 2. Considerations in Determining Breakpoints for Agent Delivered by Parenteral versus Aerosol Route

PARAMETER	PARENTERAL ROUTE	AEROSOL ROUTE
Concentration at site of infection	Intravenous and orally administered antibiotics exhibit variable penetration into CF sputum	Aerosolized agents have markedly increased endobronchial concentration
Efficiency of delivery	Predictable peak serum concentrations, but endobronchial concentrations are not predictable	Delivery efficiency to distal airways varies by nebulizer type and personal factors (such as breathing pattern, participation, posture)
Inhibition of bioactivity by CF sputum	Sputum components (e.g. glycoproteins) may bind agent	Dosage must overcome inhibitory characteristics
Toxicity	Toxicity, e.g., nephrotoxicity or ototoxicity may be avoided by monitoring serum levels	Toxicity may be unique, e.g., tinnitus and voice hoarseness and unclear if dose related

Thus, the breakpoints established for agents delivered by the parenteral route are not applicable for aerosolized antibiotics. An isolate may be labeled resistant to tobramycin, e.g., MIC >8 µg/ml, but the concentration obtained via the aerosol route will likely inhibit bacterial growth by overwhelming resistance mechanisms. Furthermore, antibiotics may also have indirect effects on bacterial growth and expression of virulence factors.

4. INCREASED MICS TO AEROSOLIZED AGENTS DO NOT IMPACT CLINICAL EFFICACY

a) TIS

It is expected that Pa will develop increasing MICs to aerosolized antibiotics. In the randomized, placebo controlled study of TIS (17), investigators analyzed several measures of antibiotic resistance that occurred from baseline to end of treatment among the Pa strains isolated from participants in the intermittent tobramycin versus placebo group. With treatment, the MIC of strains increased among th¬e tobramycin group compared with the placebo group. Similarly, the proportion of tobramycin-treated patients with Pa isolates for which the MIC was at least 8 µg/ml increased from 25% percent at week 0 to 32% at week 24, as compared with 20% at week 0 and 17% at week 24 in the placebo group.

Despite the increase in Pa tobramycin MICs, subgroup analysis demonstrated that, irrespective of the MIC of the most prevalent isolate at baseline, subjects randomized to tobramycin demonstrated improvements in lung function when compared to placebo participants. In a 72-week open-label follow-up study of TIS, changes in tobramycin susceptibility were studied among Pa isolates from 93 adolescent participants (18). After 12 cycles of TIS, the proporti¬on of isolates, as well as the proportion of patients with Pa isolates, with a tobramycin MIC of > 16 µg/ml, increased from 5% to19% and from 10% to 41%, respectively. The MIC_{50} and the MIC_{90} increased from 1 to 2 µg/ml and from 8 to 32 µg/ml, respectively. However, the increase in tobramycin MICs was not associated with a decreased clinical response. To assess the relationship between lung function and susceptibility to tobramycin, participants were grouped according to the tobramycin MIC of their most resistant P. aeruginosa isolate (< 8, 16-64, and > 128 µg/ml); the relative change in FEV_1 percent predicted among these groups was then compared. While there were small numbers of patients with isolates with the higher MIC values (n=41), there was no relationship between the MIC and the magnitude of FEV_1 response or in the proportion of participants with lung function improvement.

b) Colistin

Similar results were noted in a study conducted in the United Kingdom that assessed the effects of one month of aerosolized tobramycin compared with one month of aerosolized colistin (53). In the tobramycin arm (n=53), there was an increase in the tobramycin MICs of the Pa isolates recovered from baseline compared to Week 4. At baseline, 38% of participants had a Pa isolate with a tobramycin MIC > 4 µg/ml compared to 49% of participants at week 4 of treatment. In contrast, there was no change in the relative distribution of colistin MICs among the Pa isolates obtained from the 62 participants randomized to colistin; 55% of subjects harbored a Pa strain with an MIC to colistin of > 4 µg/ml both at baseline and at Week 4. There was no correlation between baseline Pa tobramycin and colistin MICs and changes in lung function.

c) Aztreonam

In a placebo-controlled Phase II study of inhaled aztreonam lysinate conducted among 105 participants, there was no significant change in the MIC_{50} and MIC_{90} after 14 days of treatment with either 75mg or 225 mg of aztreonam administered three times daily (54).

SECTION SUMMARY

In summary, an increase in MIC during prolonged use of an antibiotic may be observed for specific agents. The breakpoints used by clinical microbiology laboratories to establish susceptibility to antimicrobial agents are not applicable for aerosolized agents, due to differences in achievable concentrations. To date, the precise breakpoints for interpreting MICs for antibiotics delivered via aerosolization are unknown. Observations made from clinical trials have demonstrated that increasing MICs measured by antimicrobial susceptibility testing do not predict a lack of clinical response.

Thus, conventional susceptibility testing should not be used to guide use of an aerosolized agent. Rather, the clinical response to an aerosolized agent should be measured by lung function and pulmonary exacerbations.

SECTION IV. AEROSOL DELIVERY SYSTEMS

1. DEVICES

While there are many advantages to nebulized inhaled antibiotics, optimization of the delivery is based on the inhalation technique and the type of device used. A major disadvantage of conventional nebulizations is the length of time required and adherence to these treatments is variable. The nebulizer and compressor used affect the aerosol particle size and the fraction of respirable particles. Individual factors such as one's breathing pattern and volumes as well as one's anatomy and airway geometry affect the distribution of the aerosol. Therefore, appropriate education, training and strategies to help an individual with CF and their family incorporate the recommended therapies are essential.

Nebulizing liquid formulations of antibiotics has involved many different types of devices with pulmonary deposition of the dose ranging from < 1% of the charge dose in the nebulizer in infants (55) to newer systems that may deliver > 50% (56). While one of the largest clinical trials of inhaled antibiotics to date (17) used a standard nebulizer (the breath enhanced Pari LC Jet Plus), many patients use other nebulizer systems, which may result in differing levels of lung deposition. One reason for people using nonstandard nebulizers may be due to a lack of understanding of the differences in the nebulizers or compressor performance. Often, the cost of the equipment may be the issue and thus, a less expensive disposable unvented device is substituted for the reusable higher performance breath-enhanced nebulizers. Some aerosolized antibiotics are formulated to be administered in its own specially designed nebulizer (vibrating mesh nebulizers). Delivery of another medication through these specific devices will likely impact its particle size, efficiency and even the dose of the medication, thus substitution of medications in these very specific nebulizers is not recommended.

Jet Nebulizers:

Jet nebulizers depend on a high velocity jet of gas to fragment the liquid containing the antibiotics. The velocity of the gas does two things, one, it creates a partial vacuum at the top of the capillary tubes that lead to the reservoir which acts to draw up the solution and second, it imparts the energy necessary to fragment the solution into millions of tiny droplets. Variations in the velocity affect the process such that higher velocities result in both a greater rate of output and a smaller particle size distribution (57). Therefore, lower flows result in a lower rate of output and a longer nebulization time. High output rates and therefore shorter nebulization times are desirable for patients but can result in loss of medication if the patient's minute ventilation is not sufficient to keep up with this output unless a very efficient breath-enhanced or breath-activated nebulizer is used.

Compressors:

Most jet nebulizer manufacturers suggest an appropriate compressor to be used with their device. Substitution of the nebulizer and or the compressor system should be exercised with caution as it can affect the flow and aerosol particle size. Compressors in Canada are compatible with a 120-volt AC driven system. Ideally, the compressor chosen should be one that is suitable to the specification of the nebulizer and driven directly by AC electrical supply. Portable compressors that run on a 12-volt battery have a lower flow output, which can affect the nebulization particle size and time. Compressors also have an external filter that removes dust and other particles from the atmosphere before compressing it. Over time, the filters can get clogged leading to less efficient

performance of the compressor. Routine maintenance, as per the manufacturer's recommendations, is important as well as verification of operating parameters for adequate performance of the nebulizer-compressor combination.

2. MECHANISM OF ACTION OF NEBULIZED ANTIBIOTICS

The principle of pulmonary drug administration by nebulization is to achieve a compromise of creating droplets that are sufficiently small to escape the defense mechanisms of the upper airway and yet carry enough drug to be effective. The role of the nose is to remove particulate matter from the air before it can enter the lungs and it performs this role very effectively such that administration by a mask to a child breathing through the nose results in roughly half of the lung deposition as when the child is using a mouth piece (55). The recommendation for nebulized antibiotics would be through a mouthpiece when age or developmentally appropriate. For a younger child using a mouthpiece, proper supervision for the breathing technique is required.

3. NEBULIZERS AND PODHALERS

The advent of breath-enhanced nebulizers resulted in significantly more pulmonary delivery of antibiotics (58). These devices have a pair of one-way valves that entrain air into the nebulizing chamber during inspiration and force it out an expiratory valve on the mouthpiece during expiration. The entrained flow enhances nebulization so the rate of output is much greater when the patient is breathing in and the loss during expiration is much less. Not only does this result in much greater lung deposition, losses to the environment are also greatly reduced.

Another option is the breath-activated device that produces aerosol only during inspiration. These are highly efficient (56), although not necessarily fast, devices where the only source of environmental contamination is the small amount of antibiotic that has been inhaled but not deposited and leaves the patient during expiration. Because they require the patient to breathe in for activation, if the patient removes the device from his mouth, there will be no nebulization and no environmental contamination.

Finally, in an effort to reduce the burden of care, newer vibrating mesh technologies (VMT) produce a soft mist in a significantly shorter amount of time of administration. These high output nebulizers usually have a valve and a small reservoir to collect aerosol during expiration. By combining vibration (~116kHz) of a piezoelectric element with a metallic mesh membrane with thousands of microscopic holes, the liquid medication is forced through the tiny holes, which results in a uniform aerosol particle size of 2.5 µm. The eFlowTM nebulizer has already been used in clinical trials evaluating the efficacy of inhaled aztreonam and levofloxacin in CF. This system has been shown to deliver an equivalent lung dose of the 300 mg solution in 5 mL (TOBI®) within a couple of minutes compared to the Pari LC plus (59). This time saving feature of the eFlowTM of this system may increase adherence at home as well as quality of life (60). VMT is also very quiet, does not require a compressor and can run on batteries or through an electrical outlet. One disadvantage of this system is that this device is specifically designed for use with a particular agent and the performance of the device with another agent may be quite unpredictable.

Vibrating mesh technologies have further evolved and can be linked with smart computer technology, also known as adaptive aerosol delivery (AAD) such as the I-neb®. The aerosol is only delivered on inhalation during the individual's breathing. It also has the ability to adapt to one's breathing pattern so that aerosol is optimally released at a specific portion of the inspiratory time (~80%) in order to maximize particle deposition (61). However, these devices are not yet available in Canada.

The amount of drug deposited via nebulization in a patient's lungs depends on a combination of factors that include particle size distribution, size of the subject, route of administration and device performance. For infants breathing from a face mask from an unvented nebulizer the expected lung dose is < 1% of the overall dose and highly variable (55). For older children breathing through a mouthpiece, this same nebulizer results in 5 to 10% pulmonary deposition (55, 62). For the Pari LC Jet Plus that was used in the large inhaled tobramycin trial (17), deposition in the order of 15% could be expected (63). The newer version, the LC Star, would increase this (64, 65). Because there is no waste during expiration, the performance of the breath-actuated nebulizers depends only on the particle size distribution and the residual volume remaining in the nebulizer at the end of nebulization. For these devices, deposition could be as high as 50% of the charge dose for older CF patients (56). Finally, for vibrating membrane devices such as the one used in the recent Phase 1 inhaled aztreonam study, pulmonary deposition may be as high as 50% of the charge dose. In other words, unlike medication given intravenously where virtually 100% of the dose enters the patient, irrespective of the administration device, there are enormous variations in aerosol device performance so device choice is as important as the charge dose for the pulmonary delivery of a targeted amount of inhaled antibiotics.

Since 2013, TIP has become available and widely used by individuals with CF. TIP is manufactured via an emulsion-based spray-drying process that yields uniform-sized, spherical hollow porous particles (66). It is delivered via the breath-actuated T-326 Inhaler, a portable, mechanical, capsule-based dry powder inhaler. In addition to shortening use of inhaled therapy, this drug delivery system is thought to be independent of the patient's peak inspiratory flow rate, which reduces dosing variability (66). In addition to previously cited studies describing the comparable effectiveness, safety as well as the significantly reduced time administration of TIP compared to TIS (20, 21), a recent observational study involving adult patients with CF suggested that treatment adherence with TIP may be associated with improved clinical outcomes (67). Other benefits include the fact that the T-326 Inhaler used to deliver TIP is less frequently contaminated than the nebulizers, thus potentially reducing the sources of pathogenic bacteria in patients with CF (68).

4. LIMITATIONS OF AEROSOLIZATION

Even with a mouthpiece, droplets with diameters >5 μm fail to negotiate the turn at the back of the throat and deposit on the posterior pharynx. Depending on the drug, absorption can occur in the nasal cavity or in the throat and give rise to side effects but have no beneficial effects at the desired site in the lung. The fraction of the mass of an aerosol that is carried in particles small enough to deposit in the lungs if inhaled is known as the respirable fraction (RF). For adults inhaling tobramycin, deposition studies support the concept of an RF as the mass of particles = 5 μm (63). However, both in theory (69) and in practice (70), it would appear that the RF is smaller in young children with CF. One approach to this would be to design an aerosol delivery system that produced only very small droplets. The volume of the droplet and thus the amount of antibiotic carried is proportional to the 3rd power of the radius. Therefore, tiny droplets, while they may enter the lung, carry little drug and also may be exhaled. Hence a very small particle size distribution would greatly prolong the treatment time necessary to achieve a particular dose. Most aerosols today are designed to generate particles in the 1-5 μm range. For jet nebulizers, where high velocity gas shears the liquid into a wide variety of particle sizes, larger particles return to the system for re-nebulization to achieve the optimal particle size. For vibrating membrane devices, particle size is determined by a combination of pore size, frequency of vibration and the physical properties of the antibiotic solution.

Early studies looking at inhaled antibiotics (14) used unvented nebulizers, devices where a nebulizing chamber was connected to either a t-piece going to the mouthpiece or to a face mask. With these devices, the respiratory pattern of the patient had no influence on the output of the nebulizer. In practice, this meant that when the patient was breathing in, virtually all of the output of the device went into the patient (not necessarily the lungs) and when the patient was breathing out, it went into the room. Since children with CF breathing through a nebulizer circuit spend roughly 40% of the total respiratory cycle breathing in inspiration (71), this means approximately 60% of the output ends up in the room. For children breathing through a mask, antibiotics that they did not inhale entered the atmosphere from the holes in the mask or from poor fit around the nose and mouth. These unvented nebulizers are not recommended for aerosolizing of antibiotics.

SECTION SUMMARY

Although nebulized antibiotics have significantly contributed to improving clinical outcomes in CF patients with chronic airway infection, they are associated with a high treatment burden. Evolving technologies to shorten treatment times while maintaining efficacy are being studied. It is important to be well informed about the advantages and the disadvantages of the multiple nebulizer types and brands available in Canada. The type of nebulizer chosen impacts the particle size and respirable fraction. Individual factors such as one's breathing pattern (tidal volume, respiratory rate, inspiratory rate), adherence with inhalations, airway geometry and degree of lung disease will also influence the efficacy of medication deposition.

SECTION V: ADVERSE EFFECTS OF AEROSOL ANTIBIOTICS

1. AMINOGLYCOSIDES

Parenteral use of aminoglycosides is associated with well-characterized and quantifiable adverse outcomes; primarily nephrotoxicity and ototoxicity. Similar effects would be expected if drug delivered by the inhaled route were to result in significant systemic levels. While there has been broad use of IV preparations of tobramycin delivered by the aerosol route, most of the data addressing pharmacokinetic and adverse outcomes are derived from studies using the TIS formulation.

a) Systemic absorption

Pharmacokinetics/pharmacodynamics (PK/PD) analysis of inhaled antibiotics is complex given the variability in drug delivery and in mucosal absorption (upper and lower respiratory and GI tracts). Current systems are estimated to produce only ~ 10% drug mass deposition at target sites. Drug PK and bioavailability were studied by pooling data from two separate phase three studies of comparable design (72). A total of 258 paediatric and adult patients (age 6-48) receiving TIS 300 mg twice daily by jet nebulizer (Pari LC Plus) were evaluated. Sputum concentrations in the majority of the patients exceeded the MIC of the infecting Pa isolate by ten-fold. Due to the marked binding of aminoglycosides to CF sputum glycoproteins, it is thought to be necessary to exceed the MIC by 10-fold to have adequate concentrations of bioactive drug. Serum levels one hour after a 300 mg dose of TIS were low with a mean of 1 ug/ml (max 3.6 µg/ml). This is considerably lower than serum peaks achieved when tobramycin is delivered intravenously. Random levels throughout the study were generally less than the lower limit of assay detection (0.18 µg/ml). Subgroup analysis failed to show any relationship between serum concentrations and parameters such as age, gender, sputum concentration or level of airflow obstruction.

The issue of possible drug accumulation over time was addressed by repetition of serum measurements at week 20. No significant differences in levels were found from baseline. The authors went on to complete a population pharmacokinetic analysis that estimated peak and trough concentrations of 2.6 and 0.2 µg/ml respectively (72). Extrapolating from the experience with parenteral doses, this would be expected to impart minimal risk of adverse events. Limited information is available to evaluate aerosolized tobramycin pharmacokinetics in young children. Rosenfeld et al (73) measured serum concentrations in children 6 months to 6 years of age after single dosing with TIS 180 or 300 mg. Values were similar to those in adults with a mean serum peak concentration value of 0.6 µg/ml, with no measurement exceeding 2ug/ml. There was no evidence of accumulation with comparable levels measured at day 14. While reassuring, there is the possibility of inter-individual variability in systemic exposure (74). MacLusky and colleagues (14) studied 24 patients receiving aerosolized tobramycin 80 mg three times daily. Two patients had single isolated values of 5.8 and 6.5 µg/ml, whereas all other levels were <1 µg/ml. As there were no replicate measurements, assay error cannot be excluded. From the data currently available (14, 17, 73, 74), we conclude there is no compelling rational for routine serum monitoring in patients receiving doses of aerosolized tobramycin or TIS.

b) Nephrotoxicity and ototoxicity

Ramsey et al. (17) reported no change from baseline, and no difference from placebo, in serum creatinine at week 24-post administration of TIS (80.4 versus 78.7 µmol/L. A >50% increase in creatinine was reported in 9 patients, the same number reported in the placebo group. In an open label extension for 96 weeks (n= 520), no clinically significant increase in creatinine was noted (75). MacLusky et al. (14) observed no significant change in serum urea or creatinine in patients receiving tobramycin aerosolized 80 mg three times daily for 32 months. Hoffman and colleagues (76), however, reported a CF patient who developed non-oliguric renal failure temporally associated with inhaled tobramycin. While nephrotoxicity has been rarely reported with nebulized tobramycin it must be acknowledged that more sensitive measures of renal function have not been assessed and that there has been limited inclusion of high-risk CF patients (e.g. those with diabetes mellitus, renal insufficiency). These results pertain only to the doses utilized in the studies reviewed. Furthermore, given the high clearance rate of aminoglycosides in CF patients, these results cannot be extrapolated to other patient groups. Studies monitoring audiologic function in patients receiving aerosolized tobramycin have failed to establish a toxicity association (14, 15, 17, 77). Ramsey et al. (17) performed serial audiology testing on 148 patients receiving TIS at baseline 4, 8, 12 and 24 weeks. No individuals were found to have hearing loss defined as a decrease of more than 15dB in auditory threshold at two consecutive frequencies. In a 96-week open label extension of 520 subjects, none of the patients who completed follow-up had hearing loss (75). MacLusky et al. (14) reported hearing deficit in 1/15 patients receiving aerosolized tobramycin, however, this was attributed to an auditory polyp. Tinnitus has been observed in studies of inhaled tobramycin (3.1% TIS patients versus 0 in placebo), but this was generally mild in nature, transient, and in no instance lead to medication cessation (14). Patients with tinnitus did not have a concomitant hearing deficit. More sophisticated tests of vestibular function have not been reported to date in CF patients receiving aminoglycosides.

In summary, routine monitoring for nephrotoxicity or ototoxicity would not seem justified for patients receiving inhaled tobramycin. However, monitoring would seem prudent in selected cases including those with preexisting renal or auditory dysfunction, use of additional agents with potential co-toxicities, conditions with predispositions, and with considerable previous exposure to intravenous aminoglycosides. No information exists to establish the risks of aerosolized tobramycin in pregnancy.

2. COLISTIN

A number of adverse outcomes have been reported with the parenteral use of colistin. These include nausea, vomiting, neurotoxicity (paresthesias, muscle weakness, altered level of consciousness) and nephrotoxicity. There is limited data about adverse events reported with the use of aerosolized colistin. Jensen et al. only reported very briefly that inhaled colistin was not associated with bronchospasm in their study (26). Hodson and colleagues (27) reported that the incidence of adverse events in the colistin group was comparable to the TIS group. Twenty six of 53 patients (49%) treated with TIS and 22/62 (36%) treated with colistin reported at least one respiratory adverse event, with increased cough being the most common treatment-emergent event in the inhaled colistin group. They found no clinically significant changes in renal function over the 4-week study period. Schuster et al. (28) described that adverse events were similar between patients treated with dry powder colistin for inhalation and those treated with TIS. There was a higher incidence of cough (75% versus 43.5%), throat irritation (45.5% versus 28%) and abnormal taste (62.6% versus 27.5%) in the colistin group compared to the TIS group. The vast majority of adverse events was mild to moderate and resolved without sequelae. Of note, the dry powder colistin formulation is not currently available in Canada.

3. ß-LACTAMS

Most of the data regarding adverse events associated with ß-lactams are based on studies assessing the safety and efficacy of inhaled aztreonam (a monobactam) (22-24, 54). The adverse events noted in these studies consisted mostly of cough, increased sputum, dyspnea, throat irritation – all of which the authors concluded were compatible with CF disease and were not found significantly more often in treatment-groups than in placebo-groups (22-24). Allergic reactions are a potential risk for individuals exposed to aerosolization of ß-lactams.

4. LEVOFLOXACIN

According to Elborn et al., the occurrence of treatment emergent adverse events was similar between patients treated with LIS and those treated with TIS. There was a higher incidence of dysgeusia (distortion of taste sensation) in subjects treated with LIS, which accounted for the higher incidence of treatment emergent adverse events reported in at least 5% of subjects. Furthermore, treatment emergent adverse events other than dysgeusia that were reported for at least 5% more LIS subjects than TIS subjects were cough, increased sputum, paranasal sinus hypersecretion, and sinus headache. Fluoroquinolone class effects associated with systemic administration, such as nausea, arthralgia and tendonitis were uncommon (30).

Similarly, in the study conducted by Flume et al. with the exception of dysgeusia, which was only reported in the LIS group, treatment emergent adverse events were qualitatively similar between the LIS group and the placebo group during the treatment period and the entire study. Treatment-related dysgeusia was reported during the treatment period for 35.2% of LIS and no placebo patients. Excluding pulmonary exacerbations, the other most frequent treatment emergent adverse events were cough and increased sputum. Treatment emergent adverse events to discontinuation of the study for 1.8% of LIS patients and 0.9% of placebo patients; these events were disease progression and dysgeusia. Fluoroquinolone class effects associated with systemic administration were uncommon in this study as well (29).

These studies confirm adverse reactions reported in the Quinsair monograph – reporting dysgeusia as the most common side effect, occurring in more than 30% of subjects (78).

5. RISK OF BRONCHOCONSTRICTION WITH INHALED ANTIBIOTICS

For both inhaled tobramycin and colistin, adverse events include chest tightness and/or bronchospasm. Since patients with asthma or airway hyper-reactivity have been shown to develop bronchospasm after inhaling hypertonic agents, the question of the role of co-existent asthma in CF as a risk factor for bronchospasm has been raised. Preparations of these drugs formulated for intravenous use typically contain the preservatives phenol and bisulfites. More recent studies have used preservative free tobramycin preparations, which may have less of a bronchial irritating effect.

In 2002, Alothman et al. (72) investigated CF patients with either airway hyper-reactivity on spirometry or a personal/ family history of asthma. It was found that the two groups responded differently to 300 mg of preservative free tobramycin. They compared these results to CF patients with no response to bronchodilators and a negative personal or family history for asthma. For this latter "low risk" group there was a fall of 12±9% in FEV_1 following the inhalation of the preservative containing preparation but only 4±5% following the inhalation of the preservative free preparation. Since the dose of tobramycin was quite different, the suggestion was that the differences were due to non-antibiotic excipients rather than the tobramycin molecule itself. Of interest, for the

group believed to be at higher risk for bronchospasm, the fall in FEV_1 was the same for both preparations, 17±13% for the intravenous preparation and 16±12% for the preservative free solution. In all cases, the degree of bronchospasm was reversed with bronchodilators given before or after tobramycin.

With regard to colistin, the same group of investigators (77), compared the degree of bronchospasm following an inhalation challenge of 75 mg of colistin compared to an osmolarity matched saline placebo. Again, for those with an "asthmatic tendency" there was a greater fall in FEV_1 following the inhalation of colistin compared to placebo. In all cases, bronchospasm was quickly reversed with bronchodilators. It would appear that preservatives in tobramycin preparations do play a role in bronchoconstriction and that colistin itself may cause some mild bronchoconstriction. The caveat is that there was one patient in the "low risk" group who had a fall in FEV_1 of 44% following the inhalation of the preservative free tobramycin. Hence, regardless of the preparation and the inherent risk, bronchospasm can occur unexpectedly. Although the risk of bronchospasm appears to be relatively small, it is recommended that the first dose of inhaled antibiotic be given in a clinical setting, ideally where spirometry can be done pre and post administration and where healthcare personnel are present to manage any adverse events.

Nebulized vancomycin has been associated with chest tightness in a retrospective study of MRSA-positive patients from 1998 to 2008. At a dose of 200 mg four times a day for a total of 5 days, with bronchodilators, the authors state that 'a small' number of patients developed chest tightness with its use and 3 (16.6%) patients were unable to complete the full treatment course (79). In addition, Dezube et al. reported that nebulized vancomycin led to symptoms of bronchospasm in 28% of subjects receiving active drug despite pre-treatment with albuterol (43).

In many centres, bronchospasm has been minimized by mixing intravenous preparations of antibiotics (e.g. tobramycin) with salbutamol. Salbutamol does not change the activity of tobramycin (57) and the preservative in the VentolinTM Respiratory Solution, benzalkonium chloride, may lower the surface tension of the solution and thus improve nebulizer performance (80). The addition of bronchodilators is not recommended for the preservative free preparation of tobramycin (81). In addition, mixing salbutamol cannot be done with intravenous colistin. Finally, there are clinical reports that viral co-infection is associated with inhaled tobramycin induced cough/bronchospasm in patients who normally have no problem inhaling tobramycin.

6. POTENTIAL RISKS OF AEROSOLIZED ANTIBIOTICS TO OTHER PATIENTS, FAMILY MEMBERS, AND HEALTHCARE WORKERS

There are concerns that the use of aerosolized antibiotics may have environmental effects at home and in hospital. This is particularly true with the older tobramycin preparations, which contain preservatives that may induce bronchospasm in asthmatic family members, friends, or healthcare workers. In addition, there is the potential that bacteria in the environment exposed to these agents could develop resistance and subsequently cause problematic infections. There are, however, little published data to support these concerns. To the committee's knowledge, there has not been a published report of clear anaphylaxis from a bystander to an aerosolized antibiotic but caution should still be used if preservative containing preparations are used.

Environmental contamination and exposure of other persons can be minimized by careful attention to dosing and nebulization. As previously discussed, different nebulizer/compressor units deliver varying amounts of aerosol flow and thus are a factor in environmental issues. Aerosolization should be administered in a well-ventilated area to decrease potential problems.

SECTION VI. INFECTION CONTROL – CARE OF RESPIRATORY THERAPY EQUIPMENT

Infection prevention and control recommendations in CF aim to reduce acquisition of potential pathogens from patient-to-patient spread or from the contaminated healthcare environment or contaminated respiratory therapy equipment (82). Transmission from respiratory therapy devices may be due to contamination of the device itself due to improper cleaning, or from patient-to-patient transmission via a contaminated device.

To date, there are no published reports of CF patients acquiring infections from respiratory therapy equipment during home use. However, several lines of circumstantial evidence suggest that contaminated respiratory therapy equipment used in the home may play a role in acquisition or re-infection potential pathogens in patients with CF (83). More recently, Greenwood et al. studied contamination of a dry-powder inhaler compared to nebulizers and suggested that dry powder devices may have lower contamination rates (68, 84). Some of the following problems with device contamination have been noted in the literature:

- Inadequate cleaning techniques and contamination of home nebulizers with relevant bacterial pathogens (e.g., Pa) have been documented (85-88)
- In a newborn screening study, the use of aerosolized medications was associated with earlier acquisition of Pa (89)
- Cleaning and drying home respiratory therapy equipment between uses decreased the risk of acquiring Bcc (90)
- Siblings who shared respiratory therapy equipment were more likely to acquire Bcc (91)
- Tap water may harbor non-tuberculous mycobacteria, fungi, *Pseudomonas* or *Aeromonas* spp. and if tap water is used to rinse or fill a nebulizer, this could contaminate the nebulizer (92-94)
- Similarly, oropharyngeal flora could contaminate a nebulizer and be aerosolized into the lower respiratory tract
- Pneumonia in non-CF patients has been linked to bacterial contamination of multi-dose medications vials due to aerosols generated by in-line and hand-held small-volume nebulizers (82, 83)

Thus, cleaning and disinfection of reusable respiratory therapy equipment, including home nebulizers, can prevent infections in CF patients.

Nebulizers used in the home should be cleaned and disinfected using the following steps (95):

- **Step 1: Cleaning –** Complete cleaning of the equipment prior to disinfection to remove all organic and inorganic debris is required. In experimental studies, hot water and soap removed most of the bacteria that had been experimentally inoculated into the nebulizers (91). Dried or baked debris is more difficult to remove from equipment and disinfection or sterilization can become less effective or even ineffective (96, 97).

- **Step 2: Disinfection -** After cleaning, nebulizers can be disinfected (if permissible according to the manufacturer) by one of several methods described in Table 3. While acetic acid does kill Pa, vinegar has inadequate activity against some Gram-positive and some Gram-negative organisms and is no longer recommended to disinfect nebulizers (98, 99). Bleach is no longer recommended because a 0.5% hypochlorite solution did not reduce the number of CF pathogens on home nebulizers (100).

- **Step 3: Rinsing -** After disinfection, equipment should be rinsed with sterile or appropriately filtered water. In the home, sterile water can be prepared by a rolling boil for five minutes. Water processed through a 0.2-micron filter to remove bacteria is acceptable, but such filtration systems are not readily available in the home and must be maintained according to the manufacturer's recommendations. As mentioned previously, tap water may be contaminated with potential pathogens. Furthermore, Bcc may contaminate distilled water during the manufacturing process, as the manufacturing regulations for preparation of distilled water only seek to prevent contamination with coliforms (101).

Table 3. Effective Methods to Disinfect Respiratory Equipment in the Home

DISINFECTION METHOD*	RECOMMENDED DURATION	COMMENTS**
▪ Boil in water	5 minutes	If the equipment is boiled, then rinsing step can be omitted
OR ▪ Use a standard cycle dishwasher	Temperature greater than 158°F (70°C) for 30 minutes	To obtain this temperature, the dishwasher water may need to be Reset
OR ▪ Use a home microwave (2.45 Ghz)	5 minutes	
OR ▪ Steam sterilization (102)	5 minutes	At least 5 min, maximum 10 minute, at a temperature of 90°C in moist heat

* Must be permissible by the manufacturer

** Immersion (cold sterilization) in one of the following may be acceptable:
- 70-90% ethyl or isopropyl alcohol
- 3% hydrogen peroxide

There may be safety concerns if these chemicals are in a household kitchen, particularly if young children reside in the home. Furthermore, these disinfectants could be inhaled if the nebulizer is inadequately rinsed.

- **Step 4: Drying -** Air dry equipment in a clean environment after disinfection to prevent growth of microbes.

- **Step 5: Medication -** Single unit dose medication vials are always preferred, but if only multi-dose vials are available, the manufacturer's or pharmacist's recommendations for handling, dispensing and storing must be followed to avoid contamination of the vial.

In summary, CF centres should promote the use of standardized protocols to clean, disinfect, and dry respiratory therapy equipment used in healthcare settings. Patients and families should be educated routinely and regularly about proper care of such equipment in the home. Nebulizers should be cleaned and disinfected after each use.

SECTION VII. TREATMENT OF EMERGENT PATHOGENS

With the increased use of aerosolized antibiotics in patients with CF, an additional safety concern is antimicrobial selection of pathogens resistant to the aerosolized agent (103). These potential pathogens include Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative organisms such as Bcc, *Stenotrophomonas maltophilia, Achromobacter* spp. or other non-lactose fermenting gram-negative bacilli (e.g., non-aeruginosa Pseudomonas spp.), molds such as *Aspergillus* or *Scedosporium* spp., or nontuberculous mycobacteria.

In the 24-week study of TIS conducted in the U.S., investigators assessed the relative proportion of treatment emergent, intrinsically resistant organisms isolated in the tobramycin versus the placebo group (104). These investigators assessed intermittent (defined as isolation of an organism at least once during Week 2-24) versus persistent isolation (defined as isolation at Week 16, 20, and 24) of emergent organisms. Interestingly, more subjects in the placebo group had intermittent isolation of *Stenotrophomonas maltophilia* when compared with the tobramycin group **(Table 4).** An additional subgroup analysis of participants with positive cultures for *Stenotrophomonas maltophilia* demonstrated that oral quinolone usage (OR 2.7 95% CI 1.5-5.1, p≤0.01) and pre-treatment isolation of *Stenotrophomonas maltophilia* (OR 8.8 95% CI 14.4-17.1, p≤0.01), but not treatment group assignment (OR 1.02 95% CI 0.6-1.7 p=0.95), were predictors of *Stenotrophomonas maltophilia* isolation during the TIS trial (105). Aspergillus spp. were more commonly isolated from participants receiving inhaled tobramycin than from those receiving placebo **(Table 4)**; cases of allergic bronchopulmonary aspergillosis or *Aspergillus* pneumonia were not reported.

Table 4. Emergent organisms during TIS trial

ORGANISM	TOBRAMYCIN	PLACEBO
Bcc*	0.8% (2/258)	4.8% (3/262)
*S. maltophilia**	15.8% (41/258)	22.1% (58/262)
Achromobacter spp.*	7.8% (20/258)	9.5% (25/262)
Aspergillus spp.**	21.9% (43/196)	10.4% (20/193)

* Intermittent and persistent
** p≤0.01

In the study of inhaled tobramycin versus colistin conducted in the U.K., there was no emergence of Gram-negative organisms over the 4-week treatment trial in either study group (27). There was a small increase in isolation of Aspergillus spp., similar to the findings noted in the U.S. trial, but there was no associated increase in allergic bronchopulmonary aspergillosis. In addition, previous trials assessing the safety and efficacy of inhaled aztreonam for Pa infection reported that there was no change in Pa susceptibility to aztreonam; two of the studies noted that there was no selection of drug-resistant organisms (23, 24).

In summary, infection with drug-resistant organisms seems to occur infrequently during clinical trials of inhaled antibiotics, but does not appear to be associated with clinical deterioration. However, studies conducted to date have been of relatively short duration.

SECTION VIII. FUTURE DIRECTIONS

Although many antibiotics are prescribed as inhaled therapy off-label, the only inhaled antibiotics officially approved for usage in patients with CF in the US and in Canada are tobramycin, aztreonam and levofloxacin. However, some patients may not tolerate these regimens, or may continue to experience clinical worsening despite their use. As research on novel antibiotics and aerosolized formulations continues to emerge, other therapeutic options may become available for treatment of airway infections in individuals with CF. Historically, inhaled antibiotics have been used and evaluated mainly for treatment of infections caused by Pa, but recently some advancements have been made for MRSA, less so for Bcc. However, although *Staphylococcus aureus* and Pa remain the most prevalent pathogens, other organisms such as Bcc, *Achromobacter* spp. and *Stenotrophomonas maltophilia* and non-tuberculous mycobacteria are frequently encountered and may contribute to disease burden (106). There are to date no effective and approved chronic suppressive therapies for pulmonary infection with these organisms in individuals with CF.

Combination inhaled antibiotics are a promising area of research as combined therapy may achieve antimicrobial synergy while minimizing drug exposure. For example, tobramycin-based combinations would have the advantage of using a lower dose of tobramycin than tobramycin monotherapy. However, with the exception of the FTI combination previously described (25), other combinations are in experimental stages and evidence of their efficacy for infections of the CF airways is not yet available.

RECOMMENDATIONS

(For ranking system see Appendix I):

1. Inhaled TIS or NIT is recommended for use in children and adults with CF who have early or new-onset acquisition of Pa for eradication therapy. This should be decided on an individual basis (Category A; Grade I)

2. Inhaled TIS should be considered for use in persons with CF infected with Pa for chronic suppressive therapy. This should be decided on an individual basis (Category A; Grade I)

3. TIP should be considered for use in persons with CF infected with Pa for chronic suppressive therapy, as an alternative to TIS in patients who can use and tolerate the device. This should be decided on an individual basis (Category A; Grade I)

4. Aztreonam, colistin, amikacin, and levofloxacin (in adults) can be considered as alternative therapies for use in persons with CF infected with Pa for chronic suppressive therapy (Category A; Grade I)

5. For early or new-onset acquisition of Pa, eradication treatment strategies that may be utilized also include aztreonam. (Category A; Grade II)

6. High efficiency delivery systems (such as breath-enhanced or breath-activated devices) are preferable due to decreased treatment time and increased pulmonary deposition. Devices with mesh technology should be used with caution, as per manufacturers' instructions (Category A; Grade II)

7. Patients should be educated routinely and regularly by their CF care team to clean, disinfect, and air dry their nebulizer appropriately. Adherence to these recommendations should be monitored. Nebulizers should not be shared. Single use nebulizers should never be reused (Category B; Grade II)

8. If there is clinical or laboratory evidence of antibiotic-induced bronchospasm, pretreatment with beta-2 bronchodilators or co-treatment with salbutamol may be considered (Category A; Grade I)

9. Persons receiving the first dose of any aerosolized antibiotic should be monitored in a clinical setting due to the risk of bronchospasm. Consideration should be given to measuring lung function (spirometry) before and after the first dose of therapy, especially in individuals with lower lung function (Category B; Grade II)

10. Routine monitoring of serum levels of inhaled antibiotics in patients with normal renal function is not indicated. (Category A; Grade I)

11. Routine monitoring for ototoxicity is not indicated during inhaled antibiotic therapy. Please note that this recommendation does not apply to intravenous aminoglycosides. (Category A; Grade I)

12. In certain circumstances – such as pregnancy, diabetes, or renal disease – serum monitoring may be considered. (Category C; Grade III)

Appendix I – Evidence-Based Ranking System

The recommendations included in this statement are rated using five categories (A-E) to rank the strength of evidence for or against a recommendation, and three grades (I-III) to describe the quality of supportive studies **(Table 1)**. This system of rating follows guidelines that have been previously published for clinical practice guidelines. One modification to the current rating system is that in Category C the word ”insufficient“ replaces ”poor.“

By describing the strength of each recommendation and providing the quality of evidence on which the recommendation is made, the reader will be in a better position to apply the recommendations to the individual patient.

Table 1
Strength and Quality of Evidence for Recommendations

CATEGORIES FOR STRENGTH OF EACH RECOMMENDATION	
CATEGORY	**DEFINITION**
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Insufficient evidence to support a recommendation for or against use
CATEGORIES FOR QUALITY OF EVIDENCE ON WHICH RECOMMENDATIONS ARE MADE	
GRADE	**DEFINITION**
I	Evidence from at least one properly randomized controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled studies, preferably from more than one centre, from multiple time series or from dramatic results in uncontrolled experiment
III	Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies or reports of expert committees

Appendix II – Compressors

When being prescribed inhaled medication to be nebulized, the patient or family should consult with their physiotherapist or respiratory therapist. When choosing a compressor, one should consider the frequency of daily-nebulized medications, therefore a compressor that is durable, reliable and will deliver the medication in a timely manner should be selected. Portable compressors that come with batteries will increase treatment time due to a lower flow output and have shorter warranties on them. These portable compressors should mostly be considered for short-term use such as camping where access to electrical outlets may be limited or for use in other countries where the electrical voltage is different than that in Canada.

The Pari Vios Pro is a compressor made by the same manufacturer as the breath enhanced Pari jet nebulizers and it is built with a holding area for the nebulizer cup when preparing medications. The filter is in front of the machine and needs to be changed every 6 months with regular use.

Although the DeVilbiss Pulmoaide compressor is heavier and larger, it is a reliable and durable machine that has been around for decades. This is the compressor that was used in the long-term TOBI trials.

1. **Compressor Performance**

DeVilbiss Pulmo-Aide	Pari Vios Pro
Maximum pressure of compressor – 30 psi or greater	Maximum pressure of compressor – 46 psi
Maximum litre flow of compressor – 9 lpm	Maximum litre flow of compressor – 10 lpm
Operating pressure of compressor – 12-18 psi	Operating pressure of compressor – 23.2 psi (1.6 bar)
Operating litre flow of compressor for DeVilbiss Nebulizers – 5.5 lpm	Operating litre flow of compressor for Pari Nebulizers – 5.1 lpm
Electrical requirements 115V AC, 60 Hz, 1.3 A	Electrical requirements 120V AC, 60Hz, 1.5A
Power wattage – 90 watts	Power wattage – 80 W @ 23.2 psi
Weight – 7.1 lbs	Weight – 4 lbs
Warranty - 5 years	Warranty – 5 years

Should a different model of compressor be considered, the compressor specifications should be investigated to ensure that they are comparable. However, substitution of nebulizers with different compressors can affect the driving flow for the nebulizer, which is not always easy to measure. Maximum pressure (with no flow) and maximal flow (with no nebulizer) are less significant on their own.

2. **Medical Suppliers**

There are many medical equipment vendors that carry compressors. Helping to find a location that is close to the home or workplace of the individual with CF makes it more convenient for them to replenish supplies.

3. **Funding**

Each province has its own funding program that helps with the cost of purchasing medical compressors. The physiotherapist or respiratory therapist can guide individuals or families regarding eligibility and assist them with the appropriate forms. Many private health insurance companies cover the cost of compressors though may require a physician's prescription with the submission of the medical claim.

Appendix III: Summary of Products Discussed in Statement

ACTIVE INGREDIENT	PRODUCT(S)	DOSAGE	COMMENTS
Tobramycin	Nebulized intravenous tobramycin (NIT)	80-160 mg BID	Sandoz-tobramycin Preservative-free available *160 mg dosing is used in certain clinical settings, but not formally studied
	Tobramycin inhaled solution (TIS)	300 mg BID	Brand & generics available TOBI® (Novartis) Sandoz-Tobramycin Inhalation Solution Teva-Tobramycin Inhalation Solution
	Tobramycin inhaled powder (TIP)	112 mg BID	Brand only available TOBI Podhaler® (Novartis) 4 x 28 mg capsules
Aztreonam	Aztreonam inhalation solution (AIS)	75 mg TID	Brand only available Cayston®
Colistimethate	Intravenous colistin solution	75 mg BID	Generic available Sterimax-Colistimethate for Injection
	Colistimethate sodium dry powder for inhalation	1 662 500 IU BID	Not available in Canada. Colobreathe® DPI 1 x 125 mg capsule
Levofloxacin	Levofloxacin inhaled solution (LIS)	240 mg BID	Brand only available Quinsair®
Vancomycin	Nebulized intravenous vancomycin	250 mg BID	Generics available
	Vancomycin inhaled powder	30 mg BID	Not available in Canada Brand only available. AeroVanc™
Fosfomycin/ tobramycin	Fosfomycin/ tobramycin inhalation solution (FTI)	80/20 mg-160/40 mg BID	Not available in Canada
Amikacin	Amikacin Liposomal Inhalation Solution (ALIS)	590 mg OD	Arikayce® Not yet commercially available in Canada

Medication funding information, by province, is available on the Cystic Fibrosis Canada website.

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