Cystic Fibrosis

Care Guidelines Specific to
New Acquisition of Pulmonary Bacteria

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Authors

Ian Waters MD, past CF Clinic Director, Royal Jubilee Hospital (RJH), Victoria

Pearce Wilcox MD, CF Clinic Director, St. Paul's Hospital (SPH), Vancouver

Mark Chilvers MD, CF Clinic Director, BC Children's Hospital (BCCH), Vancouver

Aaron Young MD, CF Clinic Director, RJH, Victoria

Steve Kent MD, CF Clinic Director, Victoria General Hospital (VGH), Victoria

Brad Quon MD, CF Physician, SPH, Vancouver

Jodi Goodwin MD, CF Physician, SPH, Vancouver

Victoria Su PharmD, CF Pharmacy Specialist, Adult CF Clinic, SPH, Vancouver

Maggie McIlwaine PhD, CF Physiotherapist, BCCH, Vancouver

Anna Gravelle RN, MSN, CF Nurse Clinician, BCCH, Vancouver

Grant Hoffert RN, BSN, CF Nurse Clinic Coordinator, RJH, Victoria

Contributors

Robert Levy MD, Medical Director Lung Transplant Program, BC Transplant Society, Vancouver

Delane Peters RD, CF Dietitian, VGH, Victoria

Eva Co, CF Pharmacist, BCCH, Vancouver

Vanessa McMahon RN, BSN, CFNBS Nurse Clinician, BCCH, Vancouver

Hilary Vallance MD, Medical Director, BC Newborn Screening Program, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

Graham Sinclair PhD, Laboratory Head, BC Newborn Screening Program, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

Vilte Barakauskas PhD, Clinical Scientist, Division of Clinical Biochemistry, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

Benjamin Jung PhD, Division Head, Division of Clinical Biochemistry, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

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This document is based on a consensus of evidence and/or clinical expert opinion.

It is intended that this Care Pathway be reviewed and revised as needed by April 2020.

Table of Contents

General Age Range Guide

Infant	Preschool	Child	Adolescent	Adult
0 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years	≥ 18 years

Abbreviation Guide

AZLI . . . . aztreonam for inhalation solution

BAL . . . . bronchoalveolar lavage

CF . . . . . Cystic Fibrosis

CFF . . . . Cystic Fibrosis Foundation

CRP . . . . C-reactive protein

CXR . . . . Chest Xray

erm . . . . . erythromycin resistant methylase gene

FFI . . . . . Freedom from infection

HIV . . . . . human immunodeficiency virus

IV . . . . . . Intravenous

LFTs . . . . Liver function tests

LIS . . . . . levofloxacin inhaled solution

MAC . . . . mycobacterium avium complex

NTM . . . . non-tuberculous mycobacteria

OP . . . . . Oropharyngeal

PCTL . . . . Percentile

PEx . . . . . Pulmonary Exacerbation

TIS . . . . . Tobramycin Inhaled Solution

TOBI . . . . Tobramycin Inhaled Powder

Introduction

This care guideline addresses the prevention and treatment of patients with newly acquired bacteria found in respiratory specimens. Recommendations include approaches to monitoring, diagnosing, and treating, including whether or not to focus on the eradication of the bacteria.

Bacteria Specific Best Practice Recommendations

Pseudomonas aeruginosa

It has become standard practice amongst CF clinics to institute eradication regimens when Pseudomonas aeruginosa (PA) is first identified. This is based on the observation that:

- Clinical outcomes are worse in patients who are chronically infected with PA

- Evidence that culture negativity can be achieved when treatment is initiated in a timely manner after first identification.[1]

It must be acknowledged there are no properly designed studies to confirm that eradication positively impacts the future course in CF, yet given that such a strategy is commonly embraced, completing such a study is not feasible. A number of issues remain when considering and implementing eradication.

Monitoring Recommendations

1. Patients who are culture negative for PA should undergo respiratory culture every 3 months.

   ### Rationale:
   - The CF respiratory tract is vulnerable to infection with PA. PA remains the single most common organism identified in sputum cultures.

   - There is a complex adaptation of this organism in the lower respiratory tract with the result that despite a robust host response, chronic infection generally ensues.

   - However, there is an opportunity to intervene to prevent chronic infection before these adaptations occur. How long this window of opportunity lasts has not been well established and is likely to vary between individuals. Evidence suggests that this may be 6 months or greater but intuitively introduction of treatment as early as possible would seem beneficial. This must be balanced against the extra burden to patients of very frequent cultures and the costs that would be entailed.

   - The current recommendations from CF Canada and the US CFF are for patients to be reviewed in CF clinics every 3 months, and a standard part of this review is to obtain respiratory tract

cultures. While we are unaware of recommendations specific to sampling frequency for new identification of PA, we believe that this is a reasonable target on which to base eradication programs.

2. For those patients who are not able to provide an adequate expectorated sample, use the following acceptable alternatives:

- a cough oropharyngeal (OP) swab

- obtaining a sputum specimen outside of clinic, if the patient is productive (preferably with the specimen processed in a CF microbiology lab)

- an induced sputum utilizing nebulized hypertonic saline*

> *Most CF clinics would not have access to induced sputum utilizing nebulized hypertonic saline for the frequency which the tests would be required.

Rationale:

- A proportion of CF patients are not able to expectorate an adequate volume of sputum for conventional culture, particularly younger patients and those with mild lung disease. Historically, a cough oropharyngeal (OP) swab has been obtained in these individuals.

- There has been conflicting evidence in the literature as to the validity of OP cultures. Several more recent studies have compared results from a bronchoalveolar lavage (BAL), arguably the culture gold standard, with simultaneous OP cultures in stable patients.[2, 3, 4, 5] A consistency of findings has been reported with relatively high specificity (80-95%) but lower sensitivity (44-75%). The strength of an OP culture is therefore a high negative predictive value when used in a cohort with a low prevalence of PA. This was addressed in the CF Foundation Pulmonary Guideline document with the consensus that it would be better to accept a higher false negative than false positive rate (accepting arbitrarily a false positive rate of up to 10%).[6]

- Thus OP cultures have been considered acceptable in terms of performance characteristics when used for evaluation of first growth PA. The downsides of low sensitivity are more than counterbalanced by the clinical utility and applicability of this test. Future advances including culture independent techniques may improve accuracy of OP samples.

Treatment Recommendations for First Growth of PA

3. As a **first line therapy** in treating first growth of PA, use inhaled Tobramycin for 28 days.[1]

- Tobramycin Inhaled Solution (TIS) 300mg BID **or**

- Tobramycin Inhaled Powder (TOBI® Podhaler®) 112mg BID

If symptomatic at the time of first PA culture:

- Treat as per Pulmonary Exacerbation guidelines with oral or intravenous (IV) antibiotics to cover PA.

- Consider an extension with inhaled antibiotics to complete a full 28 days.

Rationale:

- While a number of eradication regimens have been studied, there is no clear consensus on the most effective one.[6, 7] Any regimen selection has to be based not only on efficacy, but additionally on safety, tolerability, practicality and cost.

- A wide range of regimens have been reported, ranging from those that are oral, inhaled, or parenteral as well as combinations thereof. However, there are very few head-to-head comparison studies making comparisons difficult given key methodological differences such as what constitutes a successful eradication.

- A treatment regimen that focuses on IV therapy has a number of potential disadvantages for CF patients and families:

  - The time commitment involved for individuals and caregivers who are often working or attending school

  - The possible adverse effects of systemic antibiotic therapy.

  - The potential for cross infection in the hospital setting (e.g. MRSA).

  When these disadvantages are coupled with the relatively high costs of hospitalization or Home IV therapy, the challenges of accessing these facilities/services along with the demonstrated efficacy of nebulized antibiotic therapies, there is a compelling argument for utilizing nebulized therapy.

- Oral medications may be less problematic than parenteral therapy but still have implications from systemic exposure.

- There would be obvious advantages if a shorter term regimen either using oral and/or inhaled antibiotics were shown to be effective. Two recent trials have addressed such regimens:

  - The Early Inhaled Tobramycin for Eradication (ELITE) study of 123 patients used either inhaled TOBI® 300mg BID for up to 56 days or a combination of TOBI and oral ciprofloxacin for 28 days. There was an eradication rate of approximately 90% that was comparable between groups. The median time to recurrence of PA was over 2 years.[8]

  - The pediatric study, EPIC – Early Pseudomonas Infection Control, used a strategy of comparing four treatment groups: cycles of TOBI® 300mg nebulizer solution BID for 28 days with ciprofloxacin or placebo for 14 days. Patients were randomized to cycled therapy every 3 months or to treatment only when pseudomonas was cultured (culture based) for a duration of 18 months. A number of endpoints were compared including time to next exacerbation, eradication rates, and lung function. The conclusions of this study were that both regimens were equally effective and there was no advantage to the addition of ciprofloxacin to TOBI®. A culture positive based approach was equivalent to the regular quarterly cycles. The median number of courses to achieve eradication was 2.[9]

- Additional studies have evaluated other regimens in smaller patient numbers.

  - Valerius et al., in a study of 26 pediatric patients, compared inhaled colistin plus oral ciprofloxacin for 3 weeks versus no treatment and reported freedom from infection (FFI) at 27 months of 86% versus 42% for the treatment and non-treatment groups respectively.[10]

- Wiesemann et al. compared inhaled Tobramycin 80mg BID continuously versus placebo for 1 year and at the end of study had FFI rates of 90% versus 20% for treatment compared to placebo groups.[11]

- Gibson et al. compared TIS (TOBI®) 300mg BID versus placebo for 28 days and found FFI rates at 56 days of 75% compared to 23%.[12]

- Taccetti et al. in 223 pediatric patients compared TIS and inhaled colistin (both groups receiving ciprofloxacin) for 28 days and found FFI for colistin (63%) and TIS (65%) comparable at 6 months.[13]

- TIS for 28 days versus inhaled colisin and oral ciprofloxacin for 3 months in 58 pediatric patients was compared by Proesmans et al. and at 24 months there was no statistical significance between groups (Colistin 61% and TIS 54%).[14]

- When considered together, these studies indicate the following:

  a. Inhaled antibiotics are effective in achieving PA eradication.

  b. Reported infection free rates are not dissimilar from reported experience with IV regimens although proper comparisons have not been completed.

  c. There is no clear preference for a specific regimen based on:

    - Inhaled antibiotics (There is insufficient data for aztreonam and levofloxacin.)

    - Duration of course beyond 28 days

  d. The addition of oral ciprofloxacin does not measurably improve eradication rates.

  e. A substantial number of patients can clear PA spontaneously.

  f. A healthy number of patients do not achieve eradication and eventual regrowth is common.

- These conclusions are similar to those based on the CFF Pulmonary Guidelines and the Cochrane Review of this topic. Note that the majority of patients studied to date were of a pediatric age and there is reason to believe that eradication rates will be less robust in adults.

4. Colistin or aztreonam can be used as alternatives to Tobramycin in treating PA.

	Dose	Notes
colistin	< 6 years old 100mg nebulized BID 6 years and older 150mg nebulized BID	Consider adding oral ciprofloxacin
aztreonam	75mg inhaled TID	

Rationale:

- There are four inhaled antibiotics employed in the treatment of chronic infection in CF (tobramycin, colistin, levofloxacin, and aztreonam).

- Eradication studies to date have focused on two of these (tobramycin and inhaled colistin) with broadly comparable outcomes. Most of the colistin protocols have also included oral ciprofloxacin. Colistin therefore represents an option for eradication treatment but likely in conjunction with oral ciprofloxacin.

- The other 2 antibiotics have more recently been released and as of yet little studied in the setting of eradication.

  - Tiddens et al., in an open label 28 day treatment regimen, examined the efficacy of aztreonam for inhalation solution (AZLI) in eradication of new onset PA.[15] This was a pediatric study enrolling 205 patients using conventional dosing 75mg TID. Successful eradication was reported in 89% of patients 28 days after the end of treatment and was 75% at 2 months. These rates are similar to those reported for TIS and colistin.

  - There is no sufficient evidence to endorse the use of levofloxacin inhaled solution (LIS) at this time.

5. If approach to PA eradication is not successful, attempt **second and third line therapy**.

   See Figure 1: Pseudomonas aeruginosa Eradication Therapy Algorithm in APPENDIX

	Antibiotic Therapy	Duration
Second Line	Inhaled Tobramycin (TIS or TOBI® Podhaler®) **or** alternate inhaled antibiotic (colistin BID or aztreonam TID) +/- oral ciprofloxacin **or** IV anti-pseudomonal antibiotics (selected based on in-vitro sensitivities) followed by inhaled antibiotics (tobramycin, colistin, or aztreonam)	Total therapy = 1 to 2 months
Third Line	IV anti-pseudomonal antibiotics (selected based on in-vitro sensitivities)	10 to 14 days
	Followed by inhaled antibiotics (suggest alternative to antibiotic previously used)	0.5 to 1.5 months Total therapy = 1 to 2 months

Note: If a patient is manifesting signs of a pulmonary exacerbation (PEx) at the time retreatment is being considered, a conventional approach for treatment of an exacerbation (see Guidelines for Pulmonary Exacerbation) should be undertaken prior to eradication treatment and should include coverage for PA. For more severe clinical presentations, utilize IV antibiotics.

Rationale:

- Experience has shown an appreciable failure rate of first attempt eradication ranging from 10 – 40%. Factors associated with failure include older age, more severe lung function abnormalities, the presence of mucoid strains of Pseudomonas and a longer duration of infection prior to initiation of treatment.[16] For these reasons one might expect lower eradication rates in adults compared to children (with most of the evidence from the younger age group), however this has yet to be properly studied.

- Currently there are no studies that provide guidance when the first eradication attempt fails. The options would be to consider the infection chronic and convert to chronic suppressive treatments or to retry eradication therapy.

- Given the negative consequences of chronic infection, we believe that a repeat attempt(s) is justified and note that this has become a standard approach in many clinics. Persistence of PA could occur because of inadequate adherence to the first treatment course so it is important in considering further strategies. Another reason for persistent infection could potentially be reinfection from the environment. Currently environmental reinfection cannot be ascertained but does require careful consideration of potential sources such as nebulization equipment.

- The EPIC trial included patients that were retreated with TIS after the initial course failed. Retreatment resulted in improved PA clearance rates making retreatment with TIS a possibility.[9]

- From basic microbiology principles, retreatment with an alternate class of antibiotics might have merit. It is also possible that IV antibiotics may reach compartments of the lung not readily reachable by inhaled antibiotics.

- Pending further direction from the literature, we propose these recommendations which in general principles are similar to the position articulated in the European CF Statement.

6. Successful PA eradication defined as a minimum of 3 negative cultures over 3 months following eradication.

   - If cultures become positive within 3 months of PA eradication, move to second line therapy.

   - If cultures become positive 3 or more months following PA eradication, repeat first line eradication therapy.

Rationale:

- There has been no consistent definition for determining success of eradication from the treatment studies published to date. This has ranged from a negative culture at the end of the eradication regimen (e.g. one month) to a requirement for repetitive cultures over 6 months.

- Any definition has to factor in the possibility of reinfection from exogenous sources which presently cannot be easily determined.

7. Molecular genotyping or culture-independent microbiological methods are not justified.

Rationale:

- At present, there is insufficient evidence to warrant these techniques. Further work is needed to determine their ultimate role in eradication evaluation.

- Several possibilities exist to account for the source of repeat positive cultures of PA after first apparent eradication.

  - Treatment related reduction in infection load such that cultures do not detect the presence of bacteria. With removal of the antibiotics, regrowth can occur and lead again to culture positivity.

  - Reinfection of the lungs from another reservoir of infection – most likely the upper airway/sinuses but also potentially the gastric microbiome. Reinfection could also occur from the same strains colonizing nebulizers that remain in use for other therapies.

  - A new infection could occur from environmental or nosocomial reservoirs.

- There is the potential to address these possibilities from developments in microbiological characterization. Culture-independent techniques have been developed and might address the possibility of persistence below the threshold of sputum positivity. However, these are not yet clinically available and bring up other issues that must be further studied such as the rate of positivity in individuals considered chronically negative (e.g. clearance rate of 'subclinical infection').

- There are methods to genotype strains of PA that could determine whether a new infecting stain is present versus a similar strain to that previously identified. At present, these are available for research application only and they would still not exclude a reinfection from the same environmental source.

Other types of Pseudomonas

1. Confirm that the non-aeruginosa Pseudomonas is persistent before considering eradication.

Rationale:

- Currently, there is insufficient evidence to recommend for or against eradication for other types of Pseudomonas.

- PA is the species that clearly predominates as a respiratory pathogen in CF, However, a number of other species are occasionally seen (e.g. P. floresens and putida). The pathogenicity of these may be variable and potentially might not be clinically significant.

Methicillin-resistant Staphylococcus aureus (MRSA)

1. Consider eradication of MRSA to prevent a chronic MRSA infection from establishing.

    ## Rationale:

    ■ Based on published studies using CFF registry data, CF patients with chronic MRSA infection appear to have worse health outcomes, including an accelerated rate of lung function loss and increased mortality compared to patients without MRSA.[17] However, MRSA is sometimes acquired in hospital and therefore patients who grow MRSA are also more likely to be sicker and have a history of frequent hospitalizations to begin with. Therefore, MRSA could just be a marker of disease as opposed to causing worse clinical outcomes. Nevertheless, the potential for adverse outcomes based on this data have provided the rationale for attempting eradication to prevent the establishment of chronic MRSA infection. However, it should be noted that no studies to date have shown that successful MRSA eradication leads to better health outcomes for CF patients.

2. Obtain repeat cultures for MRSA before attempting eradication.

    ## Rationale:

    ■ Initial detection of MRSA does not always lead to chronic infection as spontaneous clearance has been reported in up to 50% of cases in CF.[18] A recent study, which evaluated a MRSA eradication regimen (described in recommendation #3 below), demonstrated that ~30% of patients with new onset MRSA-positive sputum culture (within 6 months) were in fact MRSA negative at the time of study screening and 13% of patients with MRSA at screening, randomized to the observational control arm, were culture negative at day 28 without any treatment.[19] These data highlight the value of obtaining repeat sputum cultures prior to eradication attempts.

3. Treat MRSA using a comprehensive protocol of 2 oral antibiotics for at least 2 weeks combined with nasal, skin, and or decontamination plus 3 week environmental decontamination.

Regimen	Recommendation
Oral antibiotics	Oral Trimethoprim/Sulfamethoxazole (TMP/SMX)* + Rifampin x 14 days ■ TMP/SMX (Septra)*: 　■ Children < 40kg: 10 to 15mg/kg/day TMP PO divided BID (occasionally TID) 　■ Adults: TMP 320mg & SMX 1600mg (2 double strength Septra tablets) PO BID ■ Rifampin: 　■ Children < 40kg: 10 to 20mg/kg/day (option for liquid formulation) 　■ Adults:300mg PO BID ***Note:** If patient is Septra intolerant and > 8 years, then use minocycline 100mg PO BID
Nebulized Vancomycin (optional - can be considered based on physician discretion)	■ < 6 years old: 125mg nebulized TID post-salbutamol x 5 days ■ 6 years or older: 250mg nebulized TID post-salbutamol x 5 days
Nasal decontamination	Nasal mupirocin ointment 2% x 5 days
Skin decontamination	Whole body cleanse with chlorhexidine wipes x 5 days
Oral decontamination	0.12% chlorhexidine gluconate oral rinse gargle BID x 2 weeks
Environmental decontamination	X 3 weeks

Rationale:

■ Until recently, treatment approaches for MRSA have been anecdotal and decision-making has been supported by small studies with variable success rates. As a result, eradication was not considered standard of care.

■ While no placebo-controlled trials have been conducted to date, a recent multi-centre randomized controlled trial (n=45) demonstrated an 80% reduction in culture positivity (OP swab or sputum) at day 28 for patients randomized to treatment compared to only 26% in the observation arm.[19]

■ No randomized controlled studies have assessed eradication in the setting of chronic MRSA infection but success has been reported in a few small, uncontrolled studies in both children and adults.

4. Environment/household decontamination for MRSA should consist of:

■ Weekly washing of linens and towels.

■ Regular wiping down of high contact surfaces with chlorhexidine wipes, chlorhexidine 2 or 4% soap, or H2O2 spray.

■ Extra cleaning of airway clearance devices.

Rationale:

■ Staphylococci are hardy microorganisms that can remain viable in dry environments for periods of at least 1 week to 3 months or longer. Gram-positive bacteria are predominant in indoor dust, and most household bacteria are of human origin. Several household sources are potential sites of S. aureus contamination (e.g. door handles, pillows, bedding, clothing, carpets, sinks, taps, toilets, towels, sponges, keyboards, television remotes). As a result, the home environment can act as a potential reservoir for S. aureus and can be a persistent source for recolonization with MRSA after decolonization therapy.[20] MRSA can also be spread from family members and pets.

■ Few decontamination strategies have been tested in home environments. Recommendations are based on the only one randomized trial performed in CF to date. The randomized trial of community-acquired MRSA in children without CF did not demonstrate a significant difference in eradication success when all household members underwent eradication compared to the individual index MRSA case.[21] On this basis, there is insufficient data to recommend eradication of household members.

Burkholderia species (Burkholderia cepacia complex - BCC)

1. Any decision regarding eradication of BCC should only be made after careful review by the CF team with the patient.

Rationale:

■ In general, the Cochrane Review by Regan and Bhatt[22] concluded insufficient evidence on the topic of BCC eradication. No randomized or quasi-randomized trials were found. Data was mainly generated and collected from small case series. Treatment regimens widely varied, as did other aspects such as length of follow-up.

■ Mechanisms of resistance in BCC include: formation of a biofilm that impedes antibiotic penetration; low oxygen and iron after biofilm formation shifts bacterial growth to a slow, anaerobic growth (B-lactam kills rapid replicating bacterial, and aminoglycosides targets aerobic growing organisms); efflux pump on cell membrane; and trimethoprium-resistance dihydrofolate reductase.[23] In-vitro data suggest triple-antibiotic combination are likely more bactericidal than single or double antibiotic combination.

■ Fifty percent was resistant to single antibiotics, 8% resistant to 2-drug combinations, and all were inhibited by at least one bactericidal agent in 3-drug combination.[24]

■ In a study looking at susceptibility testing, it was found that combination of minocycline, meropenem, and ceftazidime were the most active agents.[25]

■ Meropenem plus minocycline were bactericidal against 76% of isolates; meropenem-amikacin and meropenem-ceftazidime combinations were bactericidal against 73% if isolates. Triple

combinations containing meropenem, tobramycin, and another antibiotic were bactericidal against 81-93% of isolates.[24]

- In a study testing susceptibility of antibiotics to BCC biofilms, it was found that 2-drug combinations with meropenem and high-dose tobramycin (200ug/mL), and 3-drug combinations with meropenem, high-dose tobramycin and piperacillin-tazobactam were effective in inhibiting 35% and 53% strains, respectively.[26]

- Of interest, liposomal aminoglycosides have been found to reduced MIC and enhance bacterial penetration, compared to free aminoglycosides, in an in vitro study.[27]

- A case series of 4 CF patients with new BCC acquisition described initial success in eradication following 2-week treatment with IV meropenem, tobramycin, and ceftazidime followed by 3 months of continuous nebulized TOBI®. B. multivorans strains in the report were resistant to tobramycin, SMT-TMP, colistin, and amikacin.[28]

- Another case series described 4 patients with BCC acquisition. The species was not identified in one patient while two had B.cenocepacia and one B. ambifaria. All 4 patients were given inhaled tobramycin and amiloride for 6 months. Three of the 4 patients had eradication of BCC from sputum for at least 2 years.[29]

- Unfortunately, other studies have shown conflicting results. In a small prospective study of 12 pediatric CF patients with B. dolosa, inhaled TOBI (300mg q12h) with inhaled amiloride for 24 weeks were not effective for eradication.[30] In a case series with 7 pediatric CF patients, nebulized amiloride and tobramycin were given to patients for 6 months. The combination therapy was effective for eradication of early BCC infection (within 2 months of new growth) but eradication is ineffective for chronic BCC infection.[31]

- A case report detailed successful eradication of BCC in 2 children with CF (one with B. cepacia, and another with B. gladioli). Eradication treatment was prescribed for 2 weeks with IV antibiotics followed by nebulized antibiotic for 3 months: [32]

  - IV tobramycin (10mg/kg, once daily)

  - IV Ceftazidime (50mg/kg TID)

  - IV Temocillin

  - Nebulized meropenem (250mg BID) after completion of IV antibiotics – if intolerant, switch to 3 months TOBI® Podhaler® or inhaled tobramycin solution

- A retrospective chart review was conducted in patients from BC Children's' Hospital and St. Paul's Hospital from Jan 1993 to May 2014. It included patients who grew BCC genomovars and other Burkholderia spp. Eradication was defined as ≥ 3 consecutive negative sputum cultures over 12 months:[33]

  - Eradication duration ranged from 14 to 90 days

  - Most commonly prescribed antibiotics: PO SMT-TMP, IV ceftazidime, IV meropenem

  - Eradication was successful in 4/13 patients with B. multivorans, and 2/6 with B. cenocepacia

■ The study by Horsley et al. surveyed 12 UK Adult CF centres on approaches to new BCC infection.[34] This study included 22 patients with new BCC infection from Jan 1 2002 to June 1 2011. Three cases were excluded from the study: B. cenocepacia was only identified after the patient had died, and 2 other cases were too early for assessment. Of the remaining 19 cases, 7 (37%) had successful eradication: 5 cases of B. multivorans, 1 case each of B. cenocepacia and B. vietnamiensis. Three of the 7 patients (2 with B. multivorans, and 1 with B vietnamiensis) did not receive therapy and had spontaneous clearance. The median duration of treatment was 28 days (maximum 84 days), and included combinations of 2 to 5 antibiotics. There was no correlation between antibiotic therapy and success of eradication. Generally, the centres used the following approach:

  ■ Median IV therapy of 2 weeks (range 2 to 6 weeks) with IV tobramycin and meropenem, plus SMT-TMP, ceftazidime, and chloramphenicol

  ■ Nebulized antibiotics (tobramycin or meropenem) for a median of 12 weeks

  ■ (some centres added) oral minocycline and/or oral SMT-TMP for a median of 7 (range 2 to 12) weeks

2. Given the poor clinical outcomes and/or impact of BCC on eligibility for lung transplant, consider eradicating the following strains (genomavars) of BCC:

■ B. cenocepacia

■ B. cepacia

■ B. multivorans

■ B. dolosa

Rationale:

■ There is insufficient evidence to make a definitive recommendation but the listed genomovars should be considered for eradication.

■ The prevalence of BCC in CF patients is approximately 3%: ~45% being B. cenocepacia, 40% B. multivorans, 6% B. vietnamiensis, 4% B. dolsa, and 3% B. cepacia. B. cenocepacia has been known as the cause of 'cepacia syndrome', and B. cepacia has been associated with rapid lung function decline and increased mortality. Greater risk of death post-lung transplant has been reported with B. cenocepacia. Additionally, cepacia syndrome has also been described in patients infected with B. multivorans and B. dolsa.[23]

3. Include the following antibiotics in standard antibiotic susceptibility testing for BCC:

■ Ceftazidime

■ Meropenem

■ Piperacillin-tazobactam

■ Ciprofloxacin

■ Aminoglycosides (tobramycin, amikacin)

- Aztreonam

- Sulfamethaxazole-trimethorpium (SMT-TMP)

- Tetracycline (e.g. doxycycline, minocycline)

4. For eradication treatment of BCC, use a step-wise approach consisting of IV induction therapy for 2 to 4 weeks, nebulized maintenance therapy for 3 months, and oral antibiotics during both induction and maintenance therapy.

Regimen	Recommendation
IV Induction Therapy X 2 to 4 weeks	2 to 3 IV antibiotics (meropenem, ceftazidime, tobramycin, and/or piperacillin-tazobactam) using standard dosing as per CF exacerbation therapy
Nebulized Maintenance Therapy X 3 months	Tobramycin inhaled solution (TIS) 300mg BID Alternative to tobramycin: nebulized meropenum 250mg BID
During induction and maintenance therapy	Oral antibiotic: SMT-TMP and/or minocycline

Rationale:

- It has been recommended that IV meropenem be used plus one of IV ceftazidime, chloramphenicol, SMT-TMP, or aztreonam.[23]

- Duration of total therapy is often greater than 4 weeks.

- Reports of successful eradication are available. However, given that most studies are small and retrospective in nature, it is challenging to quantify the success rate.

- No guidelines or literature are available to clearly define successful eradication of BCC. Definitions may need to be extrapolated from Pseudomonas eradication studies (see Pseudomonas section) and based on clinician's discretion.

Mycobacterium abscessus (M. abscessus)

1. When M. abscessus is present, drug susceptibility testing for regimen selection and outcome prediction is not recommended at this time.

Rationale:

- The United States Cystic Fibrosis Foundation and the European Cystic Fibrosis Society consensus recommendations:[35]

- pre-treatment testing for clarithromycin, cefoxitin, and amikacin susceptibilities

- preferably also for tigecycline, imipenem, minocycline, moxifloxacin, and linezolid

- Breakpoints for clarithromycin testing in non-tuberculous mycobacteria (NTM) were validated in human immunodeficiency virus (HIV) patients with disseminated mycobacterium avium

complex (MAC) infection and in a retrospective case series of MAC lung disease, but have not been validated in patients with Mycobacterium abscessus (M. abscessus).[36, 37, 38]

■ In a series of patients with M. abscessus lung disease, outcomes of treatment were poor and did not correlate well with in vitro susceptibilities, possibly secondary to *erm* (erythromycin resistant methylase gene) dependent inducible macrolide resistance, and relatively short durations of adequate antibiotic regimes due to interruptions due to toxicity.[39]

■ Clinical validation for susceptibility testing has been found only in a series of extra pulmonary disease in patients with mycobacterium fortuitum or chelonae and only for cefoxitin, aminoglycosides, and cotrimoxazole, but has not been reproduced in patients with M. abscessus.[40]

2. Treatment of M. abscessus should be a done in 2 phases, using polytherapy, and managed by experts in CF and non-tuberculosis mycobacterium (NTM).

Regimen	Recommendation
Intensive Phase X weeks to months*	2 IV antibiotics based ideally on sputum in-vitro sensitivities: ■ amikacin 15mg/kg/day x 2 to 12 weeks ■ 1 or more of: ■ tigecycline 50mg q12-24h ■ imipenem 500mg q12h ■ cefoxitin 2g q8h + 1 or more oral antibiotics: ■ Macrolide antibiotic - preferably azithromycin 500mg PO OD (due to increased induction of erm with clarithromycin) ■ Other considerations (see doses below in Continuation Phase) ■ minocycline ■ clofazimine ■ moxifloxacin ■ linezolid **Note:** guided by but not dictated by drug sensitivity testing

Regimen	Recommendation
Continuation Phase*	2 oral antibiotics: ■ minocycline 100mg PO BID ■ clofazimine 50 to 100mg PO OD ■ moxifloxacin 400mg PO OD ■ linezolid 600mg PO OD to BID + 1 macrolide antibiotic OD (preferably azithromycin) +/- inhaled antibiotic: ■ amikacin 500mg BID ■ liposomal 590mg OD **Note:** guided by but not dictated by drug sensitivity testing

* Duration of treatment unknown. Many patients who do not convert may still benefit from continuing or repeating treatment.[35]

Rationale:

■ There have been no randomized control trials evaluating treatment outcomes in individuals with M. abscessus pulmonary infection.

■ Long-term sputum conversion is difficult to achieve, therefore alternate goals include:

■ decreased symptoms

■ radiographic improvement

■ microbiological improvement

■ American Thoracic Society and the Infectious Disease Society of America (ATS/IDSA) guidelines are based on 1 study of 154 patients with lung disease caused by rapidly growing mycobacteria (80% M. abscessus, 6% had CF).[41] Treatment outcomes were extremely poor. Surgical resection of localized disease (not usually possible in CF), was the only effective long-term therapy for M. abscessus. Fourteen percent of patients died as a result of their NTM. However, the patients in the study did not receive the currently recommended antibiotic combinations.

■ Studies involving CF patients with M. abscessus:

■ A case report describes the successful eradication of M. abscessus in a CF patient who had alternating months of inhaled amikacin and oral clarithromycin (not commonly practiced).[42]

■ Case series to date have included 15 patients with CF and M. abscessus employing a tigecycline based regime. In these, 10/15 CF patients showed improvement.[43]

■ Other studies from non-CF patients with M. abscessus since the publication of the ATS/IDSA guidelines include:

- Sixty-five patients treated with IV amikacin + cefoxitin + PO clarithromycin + ciprofloxacin x 12 to 24 months post sputum conversion: 83% decrease in symptoms, 74% decrease in high-resolution CT scan, 58% sputum conversion and maintenance (17% of which were resistant to clarithromycin). Seventeen (22%) had resection surgery of which 88% maintained conversion.[44]

- Sixty-nine patients followed and treated x 34 months (mean) as per ATS/IDSA guidelines: 29% remained culture positive, 23% converted and relapsed, 48% converted with no relapse (57% surgical vs. 28% medical) and 16% died.39

- A follow up study looked at different response rates in different subspecies: M massiliense 88% response versus M. abscessus 25% response. All M. abscessus had functional *erm* gene versus none of the massiliense (due to an erm gene deletion, rendering it non-functional).[45]

3. Monitor patient for drug toxicity frequently and regularly during M. abscessus treatment.

Antibiotic	Tests	Frequency
Amikacin (IV)	CBC, electrolytes, Cr, CRP	1. 2nd/ 3rd dose pre and post levels 2. pre-levels bi-weekly until stable 3. weekly once stable
	Audiology	monthly
Amikacin (inhaled)	Audiology	Initially as baseline Repeat if any hearing alteration noted during treatment
	CR, GFR	After 1 month of treatment
Tigecycline	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
	Lipase	With symptoms of pancreatitis
Imipenem	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
Cefoxitin	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
Clofazimine	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
	Skin for grey-blue discolouration	ongoing monitoring
Quinolones	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
	ECG	1. pre-treatment 2. @ 1 to 2 weeks 3. q2months
Macrolides	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
	ECG	1. pre-treatment 2. @ 1 to 2 weeks 3. q2months
Linezolid	CBC, electrolytes, Cr, GFR, CRP, LFTs	bi-weekly
	Neuro assessment for neuropathy*	ongoing monitoring

*Consider pyridoxine 25 to 50mg PO OD to prevent neuropathy.

Appendix

Figure 1: Pseudomonas aeruginosa Eradication Therapy algorithm
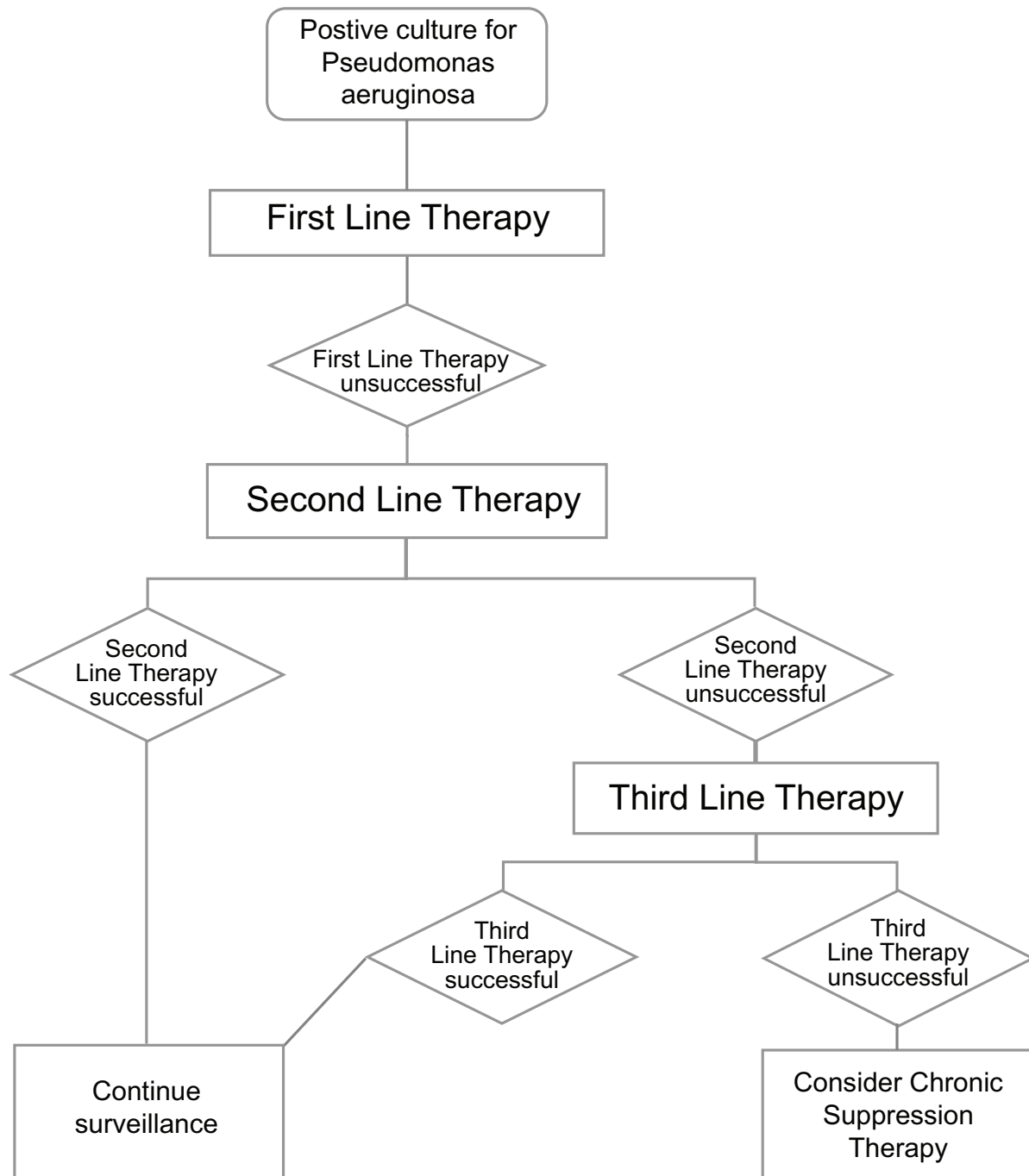
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