4.3.3 *Pseudomonas aeruginosa*

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1. INTRODUCTION

- A majority of CF patients will be chronically infected with *Pseudomonas aeruginosa* by the time they have reached the age of 20.
- CF patients may be categorized as chronically infected or intermittently infected with *P. aeruginosa*, currently free of *P. aeruginosa* infection, and never infected (**Table 1**).
- Sputum cultures (preferably deep sputum sampling, obtained during respiratory physiotherapy) should be performed at least every three months **(see also Chapter "*Clinical evaluation*", paragraph "*Microbiology*")**.
- Chronic infection with *P. aeruginosa* is associated with accelerated lung function decline, worse quality of life (QoL), increased mortality, and should therefore be treated aggressively.
- Different antibiotic treatment strategies of *P. aeruginosa* infections should be considered according to three different situations:
  - eradication therapy of a first infection or for a recurrent infection (if the patient has been free of *P. aeruginosa* infection as defined in **Table 1**)
  - chronic suppressive therapy
  - therapy of an acute exacerbation

Table 1: Patient classification according to *Pseudomonas aeruginosa* infection status (based on cultures obtained during the last 12 months)[1,2]

Chronic infection	> 50% sputum samples positive for *P. aeruginosa*
Intermittent infection	< 50% sputum samples positive for *P. aeruginosa*
Free of *P. aeruginosa*	no *P. aeruginosa* in the previous 12 months despite prior infection
Never infected	*P. aeruginosa* never cultured from respiratory samples

2. ERADICATION THERAPY

- *P. aeruginosa* has two major phenotypes: non-mucoid and mucoid **(Figure 1)**. The non-mucoid phenotype is usually found initially. Progression to the mucoid phenotype is associated with poor eradication rates.
- The time frame during which *P. aeruginosa* can be eradicated is not clearly known, but is thought to be around three months. However, the eradication therapy should be started as soon as possible.
- Several eradication therapy protocols, including inhaled antibiotic alone or in combination with ciprofloxacin, have been shown to be effective, but none seems to be more efficacious than another.

- Intravenous (IV) eradication protocols have not been properly studied, but may be considered in case of eradication failure with non-IV therapy, intolerance/allergy to inhaled antibiotics, or in more severely ill patients.
- Examples of successful eradication protocols are listed in **Table 2**. Most centers use protocols 1-3 or protocol 5. Of note, these protocols have essentially been studied in children.
- Eradication after treatment is defined as subsequent sputum cultures free of *P. aeruginosa*. The mean eradication rate of the different protocols is about 80%, but the duration of the follow-up is variable.
- To monitor the presence of *P. aeruginosa* after eradication protocols, sputum cultures should be performed at the end of treatment, one month later and every 3 months thereafter.
- In case of eradication failure, repeating the first protocol is reasonable. For those who have failed a second attempt using inhaled and/or oral antibiotics, systemic treatment with IV antibiotics may be tried.

Figure 1: a) non-mucoid and b) mucoid *P. aeruginosa* (courtesy of Dr Sudip Das, Department of Fundamental Microbiology, University of Lausanne)

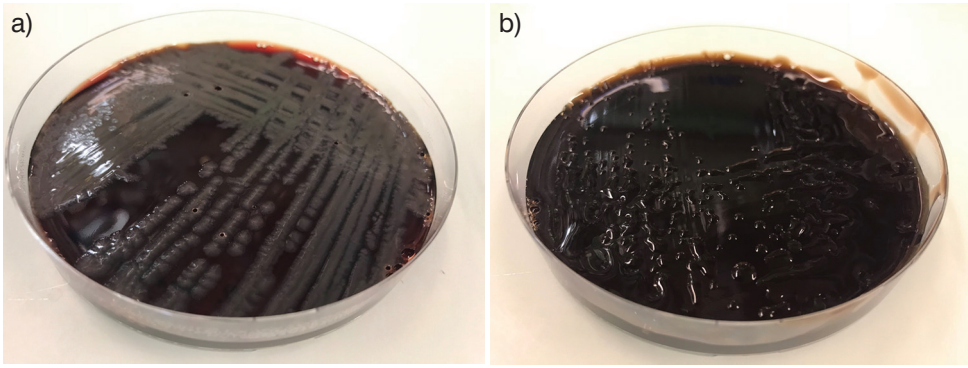

Table 2: Examples of Pseudomonas aeruginosa eradication protocols (see also [3,4])

	Antibiotic	Comments
Protocol 1[5] (4 weeks)	Tobramycin 300 mg inhaled every 12h	
Protocol 2[6] (4 weeks)	Tobramycin 300 mg inhaled every 12h + oral ciprofloxacin 15 mg/kg/day every 12h (max 750 mg twice a day) for 2-3 weeks	Addition of oral ciprofloxacin may be useful since inhaled tobramycin will not reach obstructed bronchi and/or concomitant infection in the nasal sinuses
Protocol 3[6] (4 weeks)	Colistin 2 MU inhaled every 12h + oral ciprofloxacin 15 mg/kg/day every 12h (max 750 mg twice a day)	In chronic suppressive therapy, colistin is often prescribed at 1 MU every 12h

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Protocol 4[7] (3 weeks)	Colistin 1 MU inhaled every 12h + oral ciprofloxacin 15 mg/kg/day every 12h (max 750 mg twice a day)	Increasing the duration to 3 months and the frequency of inhaled colistin to 3 times daily might be more effective
Protocol 5[8] (2 weeks)	Ceftazidime IV + tobramycine IV	Based on experience, no controlled study available*

3. CHRONIC SUPPRESSIVE THERAPY

- Chronic suppressive therapy aims to maintain the bacterial load of *P. aeruginosa* at such a low level that it is decreasing the rate of exacerbations, improving pulmonary function tests, symptoms scores, and QoL.
- Chronic suppressive therapy is recommended in chronic infection with *P. aeruginosa* and requires the use of inhaled antibiotics. This allows to reach high antibiotic concentrations in the airways, several fold higher than MIC, and to reduce systemic side effects.
- Inhaled colistin (colistimethate sodium, belonging to the group of polymyxins E) has been used for many years, sometimes on long term without interruption. It reduces *P. aeruginosa* density equally to tobramycin but may be less effective in improving lung function.
- Inhaled tobramycin and aztreonam lysine have been studied on alternate periods of 28 days (one month "on" and one month "off" = one cycle) to decrease the risk of resistance.
- Because patients complain of increased symptoms, with decreased lung function, during the "off" months, alternating regimens are often prescribed. However, combinations (e.g. tobramycin – colistin or tobramycin – aztreonam lysine) have neither been studied nor compared.
- Inhaled tobramycin in dry powder (TOBI Podhaler®) does not need nebulization, decreasing treatment duration and improving treatment adherence.
- Currently, colistin dry powder (Colobreathe®) is not available in Switzerland.
- Future inhaled antibiotic therapies in CF may include liposomal amikacin, levofloxacin and a combination of fosfomycin/tobramycin. These therapies are not yet available.

Table 3: Inhaled antibiotics for *Pseudomonas aeruginosa* chronic suppressive therapy in adult CF patients[8]

Antibiotic	Dosage	Comments
Colistin[9] Colistin® (1 MU) ColiFin Pari ® (1 MU or 2 MU)	1 -2 MU every 12h (to be reconstituted in diluent)	ColiFin® should be used with eFlow®. Not effective against Gram-positive bacteria such as *Staphylococcus aureus*. *Burkholderia cepacia* complex is naturally resistant to Colistin. Stopping colistin should be considered in patients with *B. cepacia* complex.

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Tobramycin *Solution*[10] TOBI® (300 mg/5 ml) Bramitob® (300 mg/4 ml)	300 mg every 12h	TOBI® and Bramitob® are supposed to be used with Pari LC plus nebulizer which takes 15-20 min. However, it was shown that tobramycin nebulization with eFlow® was safe, well tolerated and decreased substantially the duration of aerosol administration to ≤ 5 min.
Dry powder[11,12] TOBI Podhaler® (1 caps = 28 mg)	4 caps (powder) every 12h	TOBI podhaler® capsules should be inhaled slowly to decrease the risk of cough.
Aztreonam lysine[13,14] Cayston® (75 mg)	75 mg every 8h	Must be used with the special nebulizer (Altera) provided with eFlow®.

4. TREATMENT OF ACUTE EXACERBATION

- Acute pulmonary exacerbations in CF patients infected with *P. aeruginosa* are usually treated with a combination of two IV antibiotics directed against *P. aeruginosa.* It is common practice to combine a ß-lactam antibiotic (ceftazidime, cefepime, piperacillin-tazobactam, imipenem, or meropenem) together with an aminoglycoside (tobramycin, amikacin) or with a fluoroquinolone (ciprofloxacin). The latter can be given orally.
- Anti-pseudomonal cephalosporins and penicillins, carbapenems, aztreonam, and aminoglycosides necessitate higher doses than usual because pharmacokinetic and pharmacodynamic parameters differ between CF and non-CF individuals (**Table 4**).
- Blood concentration of ß-lactams should reach 3-4 times the MIC, and should remain above the MIC for ≥ 20-70% of the dosing interval (due to the fact that ß-lactams are time-dependent antibiotics). Thus, extended-infusion or continuous infusion (i.e. over 24h) should be favored whenever possible (**Table 5**).
- Carbapenems are not so stable and necessitate repeated dosing (in general three times per 24h).
- In contrast, aminoglycosides, such as tobramycin, are concentration-dependent antibiotics and should be administered in high doses once a day (providing the advantage of the post-antibiotic effect and allowing to avoid the adaptive effect).
- When possible, the choice of antibiotics should be based on the *P. aeruginosa* susceptibility phenotype (antibiogram). However, **multiple antibiotic resistance** (resistance to all agents in two of the main classes: β-lactams, aminoglycosides, quinolones) is frequent in adult CF patients. In these cases, the choice of antibiotics should be based on specific MIC for the given antibiotics. If not feasible, empirical therapy should combine two or three classes of antibiotics depending on the situation of the patient (e.g. β-lactam + aminoglycoside ± ciprofloxacin, in exceptional situations two β-lactams including a carbapenem and a *P. aeruginosa* active penicillin/cephalosporin can be combined or colistin IV can be added to such regimens). These combinations should be discussed with an Infectious Diseases specialist.

- Response to IV treatment may be excellent despite *P. aeruginosa in vitro* resistance. Therefore, past experience of good response to an antibiotic combination in a given patient is potentially as important as antibiotic resistance testing.
- There is a general consensus for treatment duration of 14 days.
  - **Progressive de-escalation from triple to bi- and monotherapy may be considered after 10-14 days depending on clinical response.**
  - If the clinical response is not satisfactory: consider treatment extension to 3 weeks and/or modification of the antibiotic regimen.
  - Treatment duration should not exceed 21 days, except under special circumstances.
- Monotherapy with oral ciprofloxacin is not recommended for the treatment of acute exacerbation but may sometimes be useful as a bridge to an upcoming IV cure.
- Inhaled antibiotics have not been proven to improve the efficacy of IV antibiotics for the treatment of acute respiratory exacerbations, potentially because they may not reach areas having major mucus plugs. They should not be used as the sole treatment of acute exacerbation.
- Synergy testing and multiple combination bactericidal testing of highly resistant *P. aeruginosa* are unfortunately not helpful for choosing antibiotics.
- Dosing should be adjusted to weight and renal function. Drug monitoring should be done when possible (**see Chapter "Therapeutic drug monitoring"**).

Table 4: Antibiotics for *Pseudomonas* exacerbation in adult CF patients[4,15-18]
Intermittent administration

		Antibiotic	Dosage	Comments
IV	**ß-lactams**			
	carbapenem	Meropenem	If <40kg 1.5g every 8h If >40kg 2 g every 8h	Maximum 6 g/24h
		Imipenem-cilastin	1 g every 6-8h (60-100 mg/kg/day)	Maximum 4 g/24h
	cephalosporin	Ceftazidime	3-4 g every 8h (150-250 mg/kg/day)	Maximum 12 g/24h
		Ceftazidime-avibactam*	2.5 g every 8h	
		Cefepime	2 g every 8h (100-150 mg/kg/day)	Maximum 6 g/24h
		Ceftolozane-tazobactam	3 g every 8h	
	penicillin	Piperacilline - tazobactam	4.5 g every 6-8h	Maximum 16 g/24h (of piperacillin)
	monobactam	Aztreonam	2 g every 6-8h	Maximum 8 g/24h

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	Aminoglycosides	Amikacin	30-35 mg/kg every 24h	Maximum 1.5 g/24h TDM is required
		Tobramycin	7-10 mg/kg every 24h	Maximum 660 mg/24h TDM is required
	Polymyxin	Colistin	<40kg: 1MU every 8h 40-60kg: 1.5MU every 8h >60kg: 2MU every 8h	Maximum 9 MU/24h
Oral	**Quinolones**	Ciprofloxacin	750 mg every 12h	Maximum 1.5 g/24h
		Levofloxacin	500 mg every 12h	

TDM: therapeutic drug monitoring
*At the time of writing, it is not yet available in Switzerland

Table 5: Antibiotics for *Pseudomonas* exacerbation in adult CF patients (adapted from[17,19]). Extended-infusion (i.e. over 3-4h) and continuous infusion (i.e. over 24h) administration

Antibiotic	Extended	Continuous		Comments	Thermostability at 25°C
Ceftazidime	2 g over 4h every 8h	100-150 mg/kg*	Delivered in **2** doses/day*	Max: 12 g/24h	> 24h
Piperacillin-tazobactam	4.5 g over 4h every 8h	13.5 g	Delivered in **1** dose/day	Max: 16 g/24h	> 24h
Meropenem	2 g over 4h every 8h	-	-	Max: 6 g/24h	10h
Cefepime	2 g over 4h every 8h	100 mg/kg*	Delivered in **2** doses/day*	Max: 8 g/24h	≤ 24h
Aztreonam	-	100 mg/kg	-		> 24h

*Ceftazidime and cefepime are stable for 24h at 20-25°C but their stability decreases significantly at body temperature. If these antibiotics are delivered via portable systems like CADD® pump or Easypump® II LT (Braun), an insulating cover should be used or the antibiotics should be divided in 2 doses delivered over 12h.

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