4.3.5 Other relevant bacteria

Authors: Christian Murer, Lars C. Huber, Christian Benden

1. INTRODUCTION

- Chronic pulmonary infection, defined as more than 50% culture positivity within the preceding 12 months, is a leading cause of morbidity and mortality in CF patients.
- The main bacterial pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*, but other Gram-negative bacteria including *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Inquilinus limosus*, *Ralstonia* spp., *Pandoraea apista* and anaerobic bacteria are of emerging interest.
  - Many of these bacteria have similar phenotypic characteristics rendering their identification challenging.
  - They are characterized by a wide spectrum of intrinsic and acquired mechanisms of antibiotic resistance. **Table 1** shows the profile of intrinsic resistance of *S. maltophilia* and *A. xylosoxidans*.
  - **The pathogenic relevance of these bacteria, however, remains controversial to date**.

Table 1: Intrinsic antibiotic resistance of *S. maltophilia* and *A. xylosoxidans*[1-3]

	S. maltophilia	***A. xylosoxidans***
Amoxicillin/clavulanate	R	R
Ticarcillin/clavulanate	-	-
Piperacillin/tazobactam	R	-
Cefazolin	R	R
Ceftriaxone	R	R
Ceftazidime	R	-
Cefepime	R	R
Cefuroxime	R	R
Aztreonam	R	R
Ertapenem	R	R
Imipenem	R	-
Meropenem	R	-
Linezolid	R	R
Clindamycin	R	R

(continued)

	S. maltophilia	*A. xylosoxidans*
Fusidic acid	R	R
Rifampicin	R	R
Daptomycin	R	R
Macrolides	R	R
Ciprofloxacin	-	R
Aminoglycosides	R	R
TMP/SMX	-	-
Fosfomycin	R	R
Minocycline	-	-
Tigecycline	-	-
Colistin	-	-

2. *STENOTROPHOMONAS MALTOPHILIA*

- *S. maltophilia* is an obligate aerobic, gram-negative rod, which can be found in aqueous sources.
- Like other CF pathogens, *S. maltophilia* is able to form a biofilm, which impairs phagocytosis and the penetration of antibiotic drugs.
- The prevalence of *S. maltophilia* in the lower respiratory tract of CF patients is reported between 15 to 25%.
- In one single center cohort study none of the patients shared the same strain of *S. maltophilia*, indicating that no crossinfection has occurred.
- **Outcomes:**
  - Patients with chronic *S. maltophilia* infection were found to have an increased risk of pulmonary exacerbations compared with patients without detection of *S. maltophilia* in a model adjusted for age, pancreatic insufficiency, infection with *P. aeruginosa*, body mass index and baseline lung function. Moreover, chronic *S. maltophilia* infection was associated with an almost three-fold increased risk of death or lung transplant in CF patients.
  - Conversely, no significant difference in long-term lung function was found in patients with chronic *S. maltophilia* infection compared to *S. maltophilia*-negative patients. It has also been shown that a chronic infection with *S. maltophilia* does not alter lung function recovery after a pulmonary exacerbation. Along the same line, specific antibiotic treatments (e.g. TMP/SMX or levofloxacin) did not affect the course of lung function following a pulmonary exacerbation regardless of the length of therapy.
- **In light of these data, the question whether *S. maltophilia* is a true CF pathogen or an innocent bystander remains unclear**. As such, there is no recommendation

concerning specific antibiotic therapy. In our opinion, chronic infection with *S. maltophilia* is a surrogate marker of disease severity in CF patients.

3. *ACHROMOBACTER XYLOSOXIDANS*

- *A. xylosoxidans* is an aerobic, gram negative rod found in 2 to 20% of the CF population with an increasing prevalence.
- Similar to CF patients infected with *P. aeruginosa* and *S. maltophilia*, patients with chronic pulmonary infection with *A. xylosoxidans* show biofilm-like clusters in sputum.
- **Cross-infection as a direct consequence of patient-to-patient contact has been reported.** Thus, in contrast to CF patients with *S. maltophilia* infection, we recommend to segregate these patients more strictly.
- **Outcomes:**
  - A recent study has shown that patients chronically infected with *A. xylosoxidans* compared to patients with *P. aeruginosa* infection had similar levels of inflammatory parameters and a similar rate of lung function decline one year after development of chronic infection.
- A main problem is the high rate of **intrinsic antimicrobial resistance** of the *A. xylosoxidans* species. At the moment, piperacillin/tazobactam is probably the most active anti-achromobacterial agent. Examples of protocols for the treatment of *A. xylosoxidans* are shown in **Table 2** and suggested drug doses in **Table 3**. The choice of treatment will depend on the severity of symptoms, the need of concomitant treatment for *P. aeruginosa*, the susceptibility testing results and patient drug tolerance.
- Due to the lack of more data, **the relevance of chronic infection with *A. xylosoxidans* and the role of its treatment remain unclear**.

Table 2: Examples of protocols used for the treatment of *A. xylosoxidans*[1,4,5]*

Protocol 1[4]	TMP/SMX orally and/or minocycline orally and/or chloramphenicol orally
Protocol 2[4]	Piperacillin/tazobactam IV or meropenem IV or imipenem IV or temocillin IV
Protocol 3[5]	Meropenem or imipenem + TMP/SMX or ciprofloxacin or minocycline
Protocol 4[1]	1st line: piperacillin/tazobactam, meropenem, TMP/SMX 2nd line: ceftazidime, minocycline, colistin, chloramphenicol Suggested combination: meropenem + ciproflocacin or levofloxacin Alternative combinations: - meropenem + minocycline - levofloxacin + chloramphenicol + colistin inhaled

Chloramphenicol and temocillin are not avalaible in Switzerland

*Standard treatment duration of 14 days

Table 3: Doses of antibiotics used for *Achromobacter xylosoxidans*[4-6] (in alphabetical order)

	Antibiotic	Dosage	Comments
IV	Ceftazidime	3-4 g mg every 8h (150-250 mg/kg/day)	Maximum 12 g/24h
	Ciprofloxacin	400 mg every 12h	
	Colistin	<40kg 1MU every 8h 40-60kg 1.5MU every 8h >60kg 2MU every 8h	
	Imipenem-cilastatin	1g every 6-8h (60-100 mg/kg/day)	
	Meropenem	If <40kg 1.5g every 8h If >40kg 2g every 8h	
	Piperacillin/ tazobactam	4.5 g every 6-8h	Maximum 16 g/24h (of piperacillin)
	Ticarcillin/clavulanic	3.1 g every 6-8h	Not available in Switzerland
	TMP/SMX	160-240 mg of TMP every 12h or 4-5 mg/kg of TMP every 12h	Maximum 240 mg of TMP every 12h
Oral	Chloramphenicol	500 mg every 6h	
	Ciprofloxacin	750 mg every 12h	
	Levofloxacin	500 mg every 12h	
	Minocycline	100 mg every 12h	
	TMP/SMX	160/800 mg every 8h or 320/1600 mg every 12h	
Inhaled	Colistin	1 -2 MU every 12h	

4. *INQUILINUS LIMOSUS*

- It is a gram-negative bacterium that was first identified in 1999. It has a mucoid phenotype which may contribute to colonization.
- Its clinical significance and pathogenicity are unknown but some cases of declining lung function and respiratory exacerbations have been reported.
- It has a multi-resistant profile to several antimicrobial drugs. Antibiotic susceptibility testing and concomitant infection with *P. aeruginosa* orient treatment.

  Note: susceptibility to ceftazidime, carbapenems and ciprofloxacin has been reported, but, despite treatment, in some cases *I. limosus* persisted in sputum cultures.

5. *RALSTONIA* SPP

- *Ralstonia spp* represents a group of Gram-negative bacilli, first described as a genus in 1995.
- Its prevalence in CF is not known: frequently misidentified as *B.cepacia* complex.
- Its clinical significance and pathogenicity are unknown.
- Antibiotic susceptibility testing and concomitant infection with *P. aeruginosa* will orient treatment.

6. *PANDORAEA* SPP

- *Pandoraea spp* represent a group of gram-negative bacilli described in 2000.
- Its prevalence in CF is unknown
  - It has been frequently misidentified as other species, such as *B.cepacia* complex or *Ralstonia* spp.
  - *P. apista* is the species that has been associated to CF.
- Its clinical significance and pathogenicity are unknown: some cases of declining lung function and patient-to-patient cross contamination have been reported.

7. ANAEROBIC BACTERIA

- CF-patients have a reduced mucociliary clearance and persistent mucus hypersecretion resulting in an oxygen gradient within the airways. Hypoxic regions - e.g. behind mucus plugs - provide optimal conditions for the growth of anaerobic bacteria that probably migrate from the oropharynx. Co-infection with *P.aeruginosa* might enhance the hypoxic (anaerobic) conditions.
- Anaerobic bacteria are not detected by routine culture methods thus masking the true prevalence of anaerobic infections. Following a strict anaerobic culture technique, anaerobic bacteria are detected in more than 60% of sputum samples from adult CF patients. The most frequent organisms detected are *Prevotella*, *Veillonella*, *Propionibacterium* and *Actinomyces*.
- **Outcomes:**
  - Antibiotic treatment directed against aerobe species had just a minimal effect on the abundance of anaerobe species.
  - No significant difference in lung function between anaerobe-positive vs. anaerobe-negative CF patients was found. Moreover, specific treatment has not yet been shown to have a beneficial impact on patient outcome.
- Taken together, infection with anaerobic bacteria appears to be common in CF-patients and treatment is difficult. However**, the clinical relevance of these bacteria in CF patients is not clear**.

8. *BORDETELLA* SPECIES

Authors: Angela Koutsokera, Oriol Manuel, Alain Sauty, Nicolas Müller, Christian Benden

- Pertussis ('whooping cough') is caused by the gram-negative *B.pertussis*. Other species which can cause respiratory infection are *B.parapertussis*, *B.bronchiseptica* and *B.holmesii*.

- The reported incidence of *Bordetella* positive cultures in pediatric and adult CF patients is approximately 5%. However, pertussis is probably underdiagnosed in CF because
  - diagnosis requires a high index of suspicion and specific testing
  - symptoms are non-specific and overlap with those of CF pulmonary exacerbations
  - the classic catarrhal, paroxysmal and convalescent phases may not be evident in previously vaccinated patients. Moreover, it is not known in what ways the chronic use of antibiotics (such as azithromycin or TMP/SMX) may modify the clinical manifestations or the risk of developing pertussis.
- In the general population, when symptoms last up to 4 weeks, **a nasopharyngeal swab culture and PCR** for *Bordetella* species are recommended for the diagnosis of pertussis. After 4 weeks of symptoms, **serology** is recommended mostly for epidemiological purposes. In CF the time-point of symptoms initiation may be difficult to establish.
  - Swabs used for *B. pertussis* should not contain cotton (fatty acids toxic for B. pertussis).
  - Cultures have a higher sensitivity during the first 2 weeks of symptoms (60%) but this sensitivity decreases with time and by the recent use of antibiotics. The results may take 7-10 days.
  - PCR is not affected by the use of antibiotics, is rapidly available but may be false positive.
  - Serologic testing can confirm the diagnosis of pertussis in the following situations
    - When the acute phase sampling is done early: diagnosis is confirmed by a ≥4-fold increase in the titers of IgA or IgG to pertussis toxin between the acute and the convalescent phase (i.e. 4 weeks after the acute phase sample) or
    - When the acute phase sampling was delayed: diagnosis can be established if the titer of the acute phase sample is already high (IgG anti-pertussis toxin ≥100-125 EU/ml) or if the titer decreases at a subsequent sampling after 4 weeks.
  - If results are discordant among these tests, patients should be treated for pertussis.
- Management:
  - Supportive, symptomatic care.
  - **Pertussis is highly contagious** and the following are recommended:
    a) isolation with droplet precautions until 5 days of effective treatment or after 3 weeks in untreated patients,
    b) pertussis cases should be reported to the local public health authorities,
    c) post exposure chemoprophylaxis should be considered for close asymptomatic contacts.
  - The antibiotic treatment should be started within the first 3 weeks of evolution.
    - Azithromycin orally for 5 days: 500mg 1x/day on day 1, followed by 250 mg 1x/day during days 2 to 5 or
    - Clarithromycin 500 mg 2x/day orally for 7 days or
    - TMP/SMX 800/160mg orally 2x/day for 14 days
- Vaccination **(see also Chapter "*Vaccination*")**:
  - Childhood vaccination for pertussis should be followed by booster Tdap vaccination (Boostrix®) in adulthood (1 dose at the age of 25-29). This applies for CF patients and also for close family members of CF patients.
  - Although in the current guidelines it is not recommended for the general population, CF patients may benefit from the use of Tdap (instead of Td) every 10-20 years.

9. REFERENCES

1. Abbott IJ, Peleg AY. Stenotrophomonas, Achromobacter, and nonmelioid Burkholderia species: antimicrobial resistance and therapeutic strategies. Semin Respir Crit Care Med 2015;36:99-110.
2. www.eucast.org/expert_rules_and_intrinsic_resistance
3. Wayne P. CLSI. Performance standards for antimicrobial susceptibility testing: twenty-fourth informational supplement. CLSI document M100-524. Clinical and Laboratory Standards Institute 2014.
4. McCabe D. Antibiotic prescribing guidelines in adults with cystic fibrosis. http://www.lothianrespiratorymcn.scot.nhs.uk/wp-content/uploads/2010/11/Antibiotic_guideline_final__20111.pdf.
5. Chmiel JF, Aksamit TR, Chotirmall SH, et al. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant Staphylococcus aureus, gram-negative bacteria, and multiple infections. Ann Am Thorac Soc 2014;11:1120-9.
6. Report of the UK Cystic Fibrosis Trust Antibiotic Working Group. 2009: www.cysticfibrosis.org.uk/media/82010/CD_Antibiotic_treatment_for_CF_May_09.pdf.
7. Hansen CR. Stenotrophomonas maltophilia: to be or not to be a cystic fibrosis pathogen. Current opinion in pulmonary medicine 2012;18:628-31.
8. Waters V, Yau Y, Prasad S, et al. Stenotrophomonas maltophilia in cystic fibrosis: serologic response and effect on lung disease. Am J Respir Crit Care Med 2011;183:635-40.
9. Waters V, Atenafu EG, Salazar JG, et al. Chronic Stenotrophomonas maltophilia infection and exacerbation outcomes in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2012;11:8-13.
10. Hansen CR, Pressler T, Nielsen KG, Jensen PO, Bjarnsholt T, Hoiby N. Inflammation in Achromobacter xylosoxidans infected cystic fibrosis patients. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2010;9:51-8.
11. Hansen CR, Pressler T, Ridderberg W, Johansen HK, Skov M. Achromobacter species in cystic fibrosis: cross-infection caused by indirect patient-to-patient contact. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2013;12:609-15.
12. Amoureux L, Bador J, Siebor E, Taillefumier N, Fanton A, Neuwirth C. Epidemiology and resistance of Achromobacter xylosoxidans from cystic fibrosis patients in Dijon, Burgundy: first French data. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2013;12:170-6.
13. Jones AM. Anaerobic bacteria in cystic fibrosis: pathogens or harmless commensals? Thorax 2011;66:558-9.
14. Tunney MM, Field TR, Moriarty TF, et al. Detection of anaerobic bacteria in high numbers in sputum from patients with cystic fibrosis. Am J Respir Crit Care Med 2008;177:995-1001.
15. Tunney MM, Klem ER, Fodor AA, et al. Use of culture and molecular analysis to determine the effect of antibiotic treatment on microbial community diversity and abundance during exacerbation in patients with cystic fibrosis. Thorax 2011;66:579-84.
16. Bittar F, Leydier A, Bosdure E, et al. Inquilinus limosus and cystic fibrosis. Emerg Infect Dis 2008;14:993-5.
17. Stelzmueller I, Biebl M, Wiesmayr S, et al. Ralstonia pickettii-innocent bystander or a potential threat? Clin Microbiol Infect 2006;12:99-101.

18. Jorgensen IM, Johansen HK, Frederiksen B, et al. Epidemic spread of Pandoraea apista, a new pathogen causing severe lung disease in cystic fibrosis patients. Pediatr Pulmonol 2003;36:439-46.
19. Bos AC, Beemsterboer P, Wolfs TF, Versteegh FG, Arets HG. Bordetella species in children with cystic fibrosis: what do we know? The role in acute exacerbations and chronic course. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2011;10:307-12.