4.3.4 *Burkholderia cepacia* complex

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1. INTRODUCTION

- *Burkholderia cepacia* complex (BCC) is a group of more than 17 closely related gram-negative bacteria species **(Table 1).**
- BCC is common in the environment (soil, water, rotting vegetation) and can contaminate industrial water sources**.**
- Generally, BCC is a human pathogen only in patients with CF and chronic granulomatous disease.
- BCC bacteria encode a wide range of virulence mechanisms and are inherently resistant to antibiotics.

2. EPIDEMIOLOGY

- Overall prevalence in CF patients is 2-4% and is decreasing due to better infection control measures reducing person-to-person transmission.
- Most common species of BCC seen in CF are *B. multivorans* and *B. cenocepacia.*
- Generally, BCC is associated with increased mortality including for patients who had a lung transplantation but prognosis differs for different BCC species and strains. **BCC search should be routinely done in sputum cultures of CF patients** (performed by most microbiology laboratories collaborating with CF centers).
  - BCC search requires specific culture media and can identify only the complex (i.e. BCC).
  - Identification of species and strain requires molecular typing (PCR, MLST, PFGE).
- **It is essential to determine the BCC species involved because virulence may vary according to the species and the strain, affecting prognosis, especially post-transplantation.**
  - *B. cenocepacia* is associated with worse outcomes, especially following lung transplantation and some *B. cenocepacia* strains (e.g. ET-12, CZI) may confer a higher mortality risk than others.
  - Some strains (e.g. *B. nociception* and *multivorans*) can cause acute deterioration with life threatening pneumonia and bacteriemia, called "**cepacia syndrome**".
- BCC may spread to susceptible patients through person-to-person contact, contaminated surfaces/material or the environment **(see also Chapter "*Infection control*")**.

Table 1: *B. cepacia* complex species (adapted from[1])

Species	Comments
B. cepacia	Seen in CF and non-CF patients. Associated with "cepacia syndrome"
B. multivorans	Seen in CF and non-CF patients. May be transient. Less commonly associated with "cepacia syndrome"

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B. cenocepacia	Seen in CF and non-CF patients. *B. cenocepacia* IIIA includes ET-12 and CZI strains and *B. cenocepacia* IIIB includes PHDC and Midwest clones. Associated with multiple outbreaks and "cepacia syndrome".
B. stabilis	Seen in CF and non-CF patients
B. vietnamiensis	Seen in CF and non-CF patients
B. dolosa	Seen in CF only. Associated with outbreak in CF clinic. Associated with "cepacia syndrome"
B. ambifaria	Seen in CF and non-CF patients
B. anthina	Seen in CF and non-CF patients
B. pyrrocinia	Seen in CF only
B. ubonensis	Seen in non-CF patients only
B. latens	Seen in CF only
B. diffusa	Seen in CF and non-CF patients
B. arboris	Seen in CF and non-CF patients
B. seminalis	Seen in CF and non-CF patients
B. metallica	Seen in CF only
B. contaminans	Seen in CF only. It can contaminate pharmaceutical products (e.g through contamination of compounding pharmacies) and cause outbreaks.
B. lata	Seen in CF and non-CF patients

Selective techniques (e.g. mass spectrometry MALDI-TOF) are used for the detection of BCC. Of note, from a taxonomy point of view, *B. gladioli* is not considered a member of the BCC but can cause infection in CF and non-CF patients

3. CLINICAL MANIFESTATIONS

- BCC-positive CF patients may present with
  - Colonization without change in pulmonary status.
  - Infection with accelerated pulmonary decline.
  - Cepacia syndrome (acute deterioration, life threatening pneumonia and bacteriemia).
- **Cepacia syndrome**
  - Mostly due to *B. cenocepacia* and more rarely to *B. cepacia* and *B. multivorans* infection.
  - Cepacia syndrome may occur at time of acquisition of BCC or after many years.
  - Patients usually present with fever, leukocytosis, increased inflammatory markers (C-reactive protein, ESR), patchy infiltrates or cavitary lesions on imaging.
  - Growth of *B. cepacia* species in sputum and blood cultures may take several days (initial cultures may be negative or grow other pathogens). **A high clinical suspicion should lead to early and aggressive treatment, even before microbiological diagnosis** is obtained knowing the high mortality rate of cepacia syndrome.
  - Mortality with cepacia syndrome is very high (almost 100%).

4. ERADICATION

- When a culture is positive with BCC for the first time, eradication is often attempted although there are no studies to prove effectiveness of this strategy.
- Some species of BCC (e.g. *B multivorans*) are transient and sputum culture may only be intermittently positive. Infection control guidelines suggest that this does not mean that the organism has been eradicated.

5. PREVENTION

- Prevention of BCC infection is crucial because of high level antibiotic resistance of these pathogens and because of their effect on morbidity and mortality.
- Most CF centers practice segregation to reduce the risk of transmission between CF patients in the hospital environment.
  - Hospitalized patients should always be isolated strictly (contact and droplet isolation).
  - In outpatient clinics, BCC-positive patients should be seen on different days than BCC-negative patients or at the end of the consultation program.
  - It has also been recommended that patients infected with *B. cenocepacia* should be separated from patients infected with another BCC species because *B. cenocepacia* may replace another species such as *B. multivorans.*

6. TREATMENT

- There are no randomized or quasi randomized controlled studies of the treatment of BCC so guidelines for therapy are empiric.
- BCC species exhibit innate resistance to many classes of antibiotics and this renders their treatment particularly challenging.
- Antibiotic treatment should be aggressive, combining multiple antibiotics because *Burkholderia* strains are highly resistant. The administration of high doses of antibiotics with therapeutic drug monitoring (to reach trough levels above the MIC) is recommended. **Combination of ≥ 2 antibiotics based on *in* vitro sensitivity is advocated.**
- Synergy assays for selecting the best antibiotic combination have not been shown to improve outcomes but may provide approach to combining antibiotics in therapy. If such a test was to be considered, it should be discussed with the infectious diseases consultant.
- **Duration of treatment** is not known, but aim to treat until there is clinical response and inflammatory markers back to baseline and this may take longer than the usual 14 days of therapy.
- Based on several reviews and case studies, some protocols may be proposed (depending on *in vitro* sensitivity). These protocols are presented in **Table 2**. Used antibiotics and their dosage are presented in **Table 3**.
- It is also important to treat other aspects of CF that may hinder response to antibiotic therapy (such as blood glucose control in patients with CF-related diabetes).

Table 2: Examples of treatment protocols for *B. cepacia* complex infection (adapted from[1-5])

Protocol 1[1]	1st Line	TMP/SMX, meropenem, and/or ceftazidime
	2nd Line	Minocycline or tigecycline, ciprofloxacin, piperacillin-tazobactam, ticarcillin-clavulanate, chloramphenicol
	Combine ≥ 2 agents of 1st line or 2nd line	
	In severe cases consider: Meropenem + ceftazidime + ciprofloxacin + minocycline + inhaled tobramycin	
Protocol 2[2]	TMP/SMX + minocycline for mild cases	
3rd line[4]	Aztreonam or temocillin in combination with other agents have been proposed	

Table 3: Antibiotics for *B. cepacia* complex in CF patients (adapted from[2,5-8])

	Antibiotic	Dosage	Comments
IV	Meropenem	2 g every 8h	Maximum 6 g/24h TDM may be useful
	Ceftazidime	3-4 g mg every 8h (150-250 mg/kg/day)	Maximum 12 g/24h
	Piperacillin-tazobactam	4.5 g every 6-8h	Maximum 16 g/24h (of piperacillin)
	Tigecycline	100 mg at first dose *followed by* 50 mg every 12h	
	Aztreonam	2g every 6-8h	
	Amikacin	7.5-15 mg/kg every 12h	Maximum 1.5g/24h TDM is required
	Tobramycin*	7-10 mg/kg every 24h	Maximum 660 mg/24h TDM is required
	Chloramphenicol	1 g every 6h	Not available in Switzerland. Risk of aplastic anemia
	Temocillin	1-2 g every 12h	Not available in Switzerland. Risk of cross-reactivity with penicillin and cephalosporin.
Oral	TMP/SMX	160/800 mg every 8h 320/1600 mg every 12h	
	Doxycycline	100 mg every 12h	

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	Minocycline	100 mg every 12h	
	Ciprofloxacin	750 mg every 12h	Up to 750 mg every 8h
Inhaled	Meropenem	250 mg diluted in 5 ml of NaCl 0.9% every 12h	Based on case reports and on our experience (off-label use)
	Tobramycin	300 mg every 12h	

IV: intravenous, TMP/SMX : trimethroprim/sulfamethoxazole, TDM: therapeutic drug monitoring **(see also Chapter "*Therapeutic drug monitoring*")**

* Since sputum levels of tobramycin when given IV are not high enough to effectively treat BCC, this route should not be preferred but can be combined with inhaled tobramycin in case of "cepacia syndrome"

7. TREATMENT OF "CEPACIA SYNDROME"

- Treatment protocols for cepacia syndrome are derived from case reports found in the recent literature. Some of them are summarized in **Table 4.** The optimal long-term management and antibiotic treatment of cepacia syndrome survivors is unclear.
- Although the effect of immunosuppressive drugs (corticosteroids, cyclosporine) has not been studied in this setting, they are often added to the combination of antibiotics to decrease the inflammatory host response.

Table 4: Treatment protocols used for Cepacia syndrome (adapted from[9-12])

Protocol based on	Regimen
Adult patient, non-transplanted[12]	Meropenem + tobramycin IV + TMP/SMX IV + chloramphenicol + prednisolone (30-40 mg) + cyclosporine 50 mg IV 1x/day for 5 days then 50 mg orally 1x/day At discharge (after 35 days): inhaled meropenem + cyclosporin
Adult patient, 5 years after liver/pancreas transplantation[10]	Meropenem IV + tobramycin IV + TMP/SMX IV + temocillin + inhaled meropenem + inhaled tobramycin At discharge (after 50 days): inhaled meropenem and tobramycin
Pediatric patients (n=2)[9]	Case 1: ceftazidime + meropenem + ciprofloxacine + chloramphenicol + TMP/SMX + methylprednisolone Case 2: ceftazidime + tobramycine + TMP/SMX + inhaled tobramycine + rhDNase
Our experience	Meropenem + ceftazidime IV and inhaled + tobramycin IV + TMP/SMX oral + minocycline + tigecycline + prednisone (20 mg/day) for 6 weeks

8. *B. CENOCEPACIA* AND LUNG TRANSPLANTATION

- Because mortality following lung transplantation was unacceptably high in CF patients infected with *B. cenocepacia*, some transplantation centers considered *B. cenocepacia* infection a contraindication for lung transplantation (Cepacia UK).

- However, in a French study (Boussaud et al. 2008), about 30% of patients infected with *B. cenocepacia* did survive following lung transplantation and non-cenocepacia species did not seem to confer an increased risk of mortality. Another study (Murray et al. 2008) has shown that post-transplant mortality risk may differ with different strains of *B. cenocepacia.*
- At the time of writing, in Zurich Lung Transplantation Center, infection with *B. cenocepacia* is considered an absolute contraindication for lung transplantation. At the CURT (Centre Universitaire Romand de Transplantation) the inclusion in the waiting list for lung transplantation of a CF patient colonized by *B. cenocepacia* is discussed on a case-by-case basis **(see also Chapter "*Transplantation*").**

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