Review

What is the role of *Achromobacter* species in patients with cystic fibrosis?

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1. Abstract

In recent years, advances in diagnosis and treatment have significantly modified the short- and long-term prognosis of cystic fibrosis (CF) patients. However, as in the past, the most important health problem that has significantly reduced the quality of life in CF patients is the progressive deterioration of lung structure and function. In recent years, *Achromobacter* species have emerged with increasing incidence in the respiratory secretions of CF subjects. The significance of this detection remains debated. In this review article, the characteristics of these pathogens, the importance of their presence in CF patients, and possible antibiotic treatment of treatments for colonization and infection are discussed. Literature analysis shows that *Achromobacter* species, mainly *A. xylosoxidans*, are pathogens with intrinsic characteristics that favour persistent lung colonization and several virulence factors and secretion systems that significantly interfere with respiratory cell survival. However, although it seems undebatable that *Achromobacter* species detection is a marker of CF severity, the role of these pathogens as a cause of lung structure and functional deterioration is not definitively established. Nonetheless, there is general agreement about the need for antibiotic therapy to eradicate these pathogens when they are detected in CF patients. Unfortunately, eradication is difficult, and no standard treatment is recommended by scientific societies. New possibilities are potentially offered by some recently developed drugs, such as cefiderocol, but further studies on the dosage, treatment duration and efficacy and safety of this new antibiotic in CF patients of different ages are urgently needed.

2. Introduction

In recent years, advances in diagnosis and treatment, including the use of transmembrane conductance regulator (CFTR) modulators for a subset of gene mutations [1], have significantly modified the short- and long-term prognosis of cystic fibrosis (CF) patients [2]. Survival has increased remarkably, and a large proportion of subjects who only 20 years ago would not have become adults can today reach over 50 years of age [3]. However, although life expectancy has improved considerably, the quality of life has been less modified. Many people with CF develop health complications. Poor nutrition status, diabetes, bile duct or intestinal obstruction, and mental health problems

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significantly complicate the lives of ageing CF patients [1]. As in the past, the most important health problem that significantly reduces the quality of life in CF patients is the progressive deterioration of lung structure and function due to chronic lung inflammation and the frequent recurrence of acute infectious episodes, more commonly referred to as pulmonary exacerbations [4].

Chronic colonization with bacterial pathogens is the main cause of progressive lung damage. Initially, during early childhood, traditional bacterial respiratory pathogens such as Haemophilus influenzae are the main colonizers. Later in life, the lung microbiology tends to progressively change. Staphylococcus aureus and Pseudomonas aeruginosa become dominant and are the main cause of all infectious respiratory clinical problems in CF patients. However, all national CF registries clearly indicate that in recent years, other microorganisms, including Achromobacter (Ac) species, have emerged and can be detected with increasing incidence in the respiratory secretions of CF subjects, highlighting the continuous modification of CF respiratory microbiota. Although the reasons for these changes are not precisely defined, it seems likely that the improved methods of bacterial identification, use of antibiotics, infection control practices, increasing prevalence of individuals with milder disease, and survivor effect may play a role in this regard [5, 6].

Ac species are opportunistic pathogens that have been associated with the development of severe infections, such as bacteraemia, endocarditis, pneumonia, and peritonitis [7–11]. Despite this fact, the significance of the detection of these bacteria in CF patients remains debated. It is not precisely defined whether they play a role as a cause of a more rapid deterioration of lung structure and function or they simply represent a sign of severe CF disease. In this paper, the characteristics of these pathogens, the importance of their presence in CF patients, and possible antibiotic treatment for colonization and infection will be discussed.

3. Achromobacter species

3.1 Characteristics

Ac species are gram-negative, lactose nonfermenting, catalase- and oxidase-positive bacilli that are classified as aerobic organisms, although they may also thrive in anaerobic conditions [12]. They are widely distributed in moist environments and soil and are increasingly found in hospital settings where they can be diffused through contaminated fluids. A total of 21 Ac species have been identified [12]. The most frequent isolate in CF patients worldwide is *A. xylosoxidans*, followed by *A. ruhlandii*. Other species isolates from chronic and occasional lung infection in CF patients are *A. insuavis*, *A. deleyi*, *A. denitrificans*, *A. insolitus*, *A. pestifer*, *A. spanius* and *A. marplatensis*. However, as the differentiation of different species requires specific molecular-based methods, the true frequency of the various species in CF patients remains poorly defined [13]. Generally, Ac species isolated with conventional methods are reported as *A. xylosoxidans* [14, 15].

Similar to *P. aeruginosa*, Ac species possess a number of intrinsic characteristics that may explain both their long-term presence in the lung microbiome and their potential ability to damage lung structure and function. Their genome is highly dynamic, and hypermutation can favour adaptation of the pathogen to the lung environment and persistent colonization/infection [16]. Ac species possess a number of protein secretion systems that allow them to deliver lethal toxins into bacterial cells [17, 18]. They are resistant to natural antimicrobial peptides contained in airway secretions [19]. Finally, they exhibit significant motility and a great ability to adhere to respiratory cells and to form biofilms, all characteristics that are important determinants of persistence, reduced sensitivity to natural defences and antibiotic activity [20, 21].

3.2 Achromobacter species sensitivity to antibiotics

Bacteria included in the Ac genus are generally multidrug resistant pathogens [22]. This is because they possess several intrinsic and acquired resistance mechanisms that frequently simultaneously work to make antibiotics currently used against gram-negative rods completely ineffective both *in vitro* and *in vivo*. Efflux mechanisms, beta-lactamase production and mutations in target proteins are antibiotic resistance determinants in Ac species [22]. Three different efflux mechanisms have been described. AxyABM is responsible for resistance to cephalosporins (except cefepime and cefuroxime), aztreonam, nalidixic acid, fluoroquinolones, and chloramphenicol [23]. AxyXY-Oprz makes aminoglycosides, cefepime, carbapenems, some fluoroquinolones, tetracyclines, and erythromycin ineffective [24, 25]. Finally, AxyEF-OprN extrudes some fluoroquinolones (levofloxacin and ciprofloxacin), tetracyclines (doxycycline and tigecycline) and carbapenems (ertapenem and imipenem) [26]. All the efflux mechanisms are intrinsic and detectable in most of the Ac species that are commonly encountered in CF patients. Only some strains that rarely colonize these subjects do not carry the AxyXY-Oprz efflux mechanism and remain sensitive to aminoglycosides. The production of beta-lactamases may be intrinsic (as in the case of OXA114, which makes piperacillin, ticarcillin, cephalothin and benzylpenicillin totally ineffective [27]) or acquired (such as extended-spectrum beta-lactamase [ESBL] and AmpC, which inactivate all beta-lactam antibiotics except carbapenems [28–30]). Intrinsic or acquired beta-lactamases can ultimately comprise plasmidic and chromosomal carbapenemases that generally hydrolyse all beta-lactams except aztreonam [28–30]. However, strains carrying VIM-2 beta-lactamase are also resistant to aztreonam [31–34].

Due to the different distributions of resistance mechanisms among Ac species and within the same species, minimum inhibitory concentration (MIC) breakpoints for these pathogens have not been definitively established. Only recently have clinical minimal inhibitory concentration breakpoints for several antibiotics been proposed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [35]. Moreover, sensitivity to antibiotics can significantly vary from strain to strain and seems to gradually decrease, probably because of within-host bacterial genome evolution during chronic colonization [36]. This can explain why studies carried out in different countries and in different periods of time have reported different results. The global evaluation of nine case series published from 2003 to 2014 showed that the most effective *in vitro* antibiotics were ticarcillin (99.5%), cefoperazone-sulbactam (98.7%), piperacillin-tazobactam (97.2%), and imipenem (86.4%), whereas aztreonam and tetracyclines displayed poor sensitivity (1.5% and 17.5%, respectively) [37]. In a study carried out in Argentina in which 59 strains of Ac species were collected from clinical specimens of patients, similar to what had been previously reported by other authors [38, 39], the most active antibiotics were piperacillin alone or with tazobactam and carbapenems, with meropenem significantly more effective than imipenem and ertapenem [40]. Co-trimoxazole, minocycline, and colistin were at least partially active. Among cephalosporins, ceftazidime was more effective than cefepime [40]. In UK, in a sample of 112 Ac spp. from CF patients, piperacillin-tazobactam (70.2%) and cotrimoxazole (69.7%) were the most active antibiotics [41]. Finally, in France, colistin was found to be effective in 19 out of 22 Ac strains collected from CF patients [42].

Combinations of antibiotics were found to exert a synergistic interaction that in some cases significantly increased the bactericidal activity of the single agent, providing evidence for potentially effective *in vivo* therapies. A very good example in this regard has been reported by Daman-Çelik *et al*. [43]. These authors tested meropenem alone or in combination with colistin, levofloxacin, and chloramphenicol and found that when meropenem was combined with colistin, the combination was effective against bacteria susceptible to meropenem and colistin but also against colistin resistance. In contrast, the meropenem-levofloxacin combination had a synergistic but not bactericidal effect, whereas the meropenem-chloramphenicol combination was neither synergistic nor bactericidal [43].

4. Achromobacter species in patients with cystic fibrosis (CF)

4.1 Frequency of detection

In the last 20 years, Ac species have been detected with increased frequency in the respiratory secretions of CF patients [44]. Several factors could explain the emergence of these pathogens [45, 45]. The use of aggressive antibiotic therapy in an attempt to eliminate typical CF pathogens, such as *S. aureus* and *P. aeruginosa*, may have strongly induced bacterial selection. Evidence of Ac species may also have been favoured by the introduction in clinical practice of advanced bacterial detection methods, more careful CF patient follow-up, and prolongation of the average lifespan. Finally, it cannot be excluded that the increased detection may be ascribed to some Ac species characteristics, mainly constitutive resistance to many antibiotics and the ability to adapt to surrounding pressures by means of within-host genome evolution, all factors that may favour persistence in respiratory secretions [44–46].

Despite detection in almost all studies, the incidence of Ac species identification in CF patients varies significantly from study to study, ranging from 3% to 30% [47–49]. The criteria used to define colonization (sporadic, intermittent, or chronic) and the time of evaluation can explain the differences. The lowest values were associated with chronic colonization and with collection of respiratory samples in the first years of this century [50]. A study carried out in France clearly showed that the detection of Ac species in respiratory secretions of CF patients increased from 1999 to 2018 from 3.1% to 6.7% [51]. Similar data have been collected in the USA [52].

4.2 Clinical relevance

The clinical relevance of Ac species in CF patients remains debated. Several retrospective studies have shown that CF patients with severe disease are more frequently infected by *A. xylosoxidans* than are patients with less severe signs and symptoms of lung involvement [53–55]. Worse lung function, more frequent pulmonary exacerbations and the need for hospitalization and antibiotic treatment were more common among *A. xylosoxidans*-infected patients than among noninfected controls [53–55]. This explains why the detection of this pathogen in a CF patient is considered a marker of severe CF. However, as few studies for species other than *A. xylosoxidans* exist, the greater clinical relevance of this pathogen is not definitively established. On the other hand, the role of Ac species infection as a cause of primary deterioration of lung function is far from definitively ascertained. Support for this hypothesis is given by the evidence that Ac species can cause a significant inflammatory status similar to that caused by *P. aeruginosa* and are potentially able to cause progressive lung damage per se. Hansen *et al*. measured cytokine levels in the serum and sputum of 11 healthy controls and 60 CF patients, 11 with *A. xylosoxidans*, 11 with the *B. cepacia* complex, 21 with *P. aeruginosa* and 17 without infection with these pathogens [56]. They found that all of the chronically infected patients had significantly higher serum levels of interferon (IFN)-γ and interleukin (IL)-6 than noninfected CF patients. However, only *A. xylosoxidans* and *P. aeruginosa*

patients had significantly higher sputum tumour necrosis factor (TNF)-α and serum granulocyte colony stimulating factor (G-CSF) levels, suggesting that these bacteria could cause greater lung damage.

Clinical findings do not definitively solve the problem of the causative role of Ac species. Indeed, data collected in several studies have not answered this question. In one investigation, respiratory function and exacerbation frequency were compared in CF patients with at least one sputum culture positive for *A. xylosoxidans* and in control uninfected patients [57]. Data collected between 1 year prior to and 3 years after *A. xylosoxidans* isolation were considered. Compared to negative patients, positive subjects showed a greater decline in forced expiratory volume in 1 second (FEV1) in the first year (–153.6 $\pm$ 16.1 mL·year^{-1} vs. –63.8 $\pm$ 18.5 mL·year^{-1}; p = 0.0003), together with more exacerbations in the first 3 years after pathogen detection (9 vs. 7; p = 0.03). However, these findings do not definitively demonstrate a causal relationship between the presence of the pathogen and the worsening of pulmonary disease because the subjects with *A. xylosoxidans* had, at the beginning of the study, a worse clinical situation and greater FEV1 decline, and more exacerbations were mainly evidenced in *A. xylosoxidans* cases co-colonized with *P aeruginosa* (75%) [56]. Similar inconclusive findings were reported by Edwards *et al*. [58], Firmida *et al*. [59], Somayaji *et al*. [55], and Marsac *et al*. [60]. The first authors found that if CF patients were more likely to experience pulmonary exacerbation with incident Ac species-positive cultures (42% vs. 21%; odds ratio [OR], 2.7; 95% confidence interval [CI], 1.1–6.7; p = 0.03), persistent infection was associated with neither annual lung function decline (–1.08% [95% CI, –2.73 to 0.57%] vs. –2.74% [95% CI, –4.02 to 1.46%]; p = 0.12) nor the risk of pulmonary exacerbations (OR, 1.21 [95% CI, 0.45 to 3.28]; p = 0.70) [55]. In a case-control retrospective study, the clinical course of a group of chronically or intermittently *A. xylosoxidans*-colonized/infected CF patients was compared with that of never colonized/infected subjects during two periods that were 2 years apart [61]. No differences in lung function among groups over 2 years were evidenced, although in the chronically colonized/infected subjects, a trend towards a greater decrease in lung function was observed (51.7% in the chronic colonization/infection group vs. 82.7% in the intermittent colonization/infection group vs. 76% in the never colonized/infected group) [55]. Somayaji *et al*. [55] studied 88 patients who had one or more cultures positive for Ac species during the course of 18 years. They found that pulmonary exacerbations and risk of death or transplantation were more common in these subjects than in uninfected CF patients. However, further evaluations did not show any independent association between chronic Ac species infection and worsening of the risk of pulmonary exacerbation, lung function deterioration or the time lag for death or lung transplantation. Finally, a recent case control study by Marsac et al. carried out in two French paediatric centres compared 45 patients infected by *A. xylosoxidans* with the same number of never infected controls matched for age, sex, pancreatic status and genotype [60]. Clinical data collected in the two years immediately preceding and following the first identification of the pathogen were evaluated. CF severity was significantly greater in *A. xylosoxidans* patients than in controls both before and after pathogen detection. Pulmonary exacerbations, hospitalization, and the need for antibiotic courses were significantly more frequent in positive than in negative patients. Moreover, lung function decline tended to be faster in cases (–5.5% vs. –0.5% per year). However, even in this study, the greater colonization with *Pseudomonas aeruginosa* in *A. xylosoxidans*-positive patients (p = 0.0002) makes these findings difficult to interpret [60].

5. Treatment of patients with cystic fibrosis (CF) and Achromobacter species colonization or acute exacerbation

Similar to what has been reported for *Pseudomonas aeruginosa* [61] and *Burkholderia cepacia* complex [62], for Ac species, transmission of these pathogens between CF patients has also been demonstrated [63]. This means that to avoid Ac species infection, close contact between chronically infected patients and noninfected patients should be avoided. No standard treatment for Ac species eradication in CF patients is presently recommended by scientific societies. Several other factors besides the already cited differences in sensitivity to antibiotics among Ac species can explain this limitation. The total number of patients with Ac species infection enrolled in studies evaluating the efficacy of antibiotic therapy in CF patients is too small to draw definitive conclusions. Coinfection with other pathogens, such as *P. aeruginosa*, can significantly hamper antibiotic treatment efficacy evaluations. The role of the addition of inhaled antibiotics to standard systemic therapy in Ac species eradication is not definitively established, although a study has shown that 56% of patients who received inhalation therapy with ceftazidime, colistin, or tobramycin were not colonized by Ac species after three years, compared to 13% of patients who were not given inhaled antibiotics [64]. All these findings seem to suggest that treatment of Ac species infection in CF patients should be evaluated on a case-by-case basis, considering the patient medical history, frequency of respiratory exacerbations, infection severity, antibiotics previously administered, and *in vitro* antibiotic susceptibility of previous and current infecting bacteria. However, while waiting for a microbiological response, as generally suggested for pulmonary exacerbations in CF patients with possible multiresistant pathogens, prescription of a combination therapy including carbapenems is considered the best solution [65, 66]. Some suggestions for initial therapy can

also be drawn from some studies carried out in patients experiencing Ac species infections cited outside the context of CF [67]. In a group of 34 trauma patients with a total of 37 episodes of Ac species-related ventilatory associated pneumonia, clinical success was achieved in 87% of the cases using imipenem/cilastatin, cefepime, or cotrimoxazole [68]. Moreover, most of the patients with *A. xylosoxidans* bacteraemia receiving ceftazidime, piperacillin, ticarcillin and cotrimoxazole given alone or in combination had a positive evolution [69]. Finally, ceftazidime was effective in patients with *A. xylosoxidans* meningitis [70]. However, it must be highlighted that the results of that study remain debatable as, together with antimicrobial drugs, other therapeutic interventions that may have played a role in favouring infection eradication were simultaneously put in place. In bacteraemic patients and in subjects with meningitis, central venous catheters and epidural catheters were removed [69, 70]. On the other hand, administration of piperacillin-tazobactam, meropenem, and imipenem monotherapies to a group of elderly people with hospital-acquired pneumonia due to Ac spp. was only partially effective, as 5 out of 15 patients died on Day 30 of treatment [71].

A valuable contribution to the effective treatment of Ac species infection may be offered by cefiderocol. This is a new-generation parenteral siderophore cephalosporin that, as with other beta-lactam antibiotics, acts by inhibiting bacterial cell wall synthesis [72]. However, it has increased bacterial killing properties, as it exhibits improved stability to beta-lactamases and is actively taken up by gram-negative bacteria under iron-depleted conditions [73]. This drug has been found to be effective *in vitro* against a great number of gram-negative rods, including multidrug-resistant Enterobacteriaceae and nonfermenting organisms [74]. Data regarding Ac species are limited, but some evaluations have reported very low minimum inhibitory concentrations, suggesting potentially high therapeutic activity in severe infections due to this pathogen [74]. Cefiderocol is approved by the Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in adults when these diseases are caused by gram-negative bacteria resistant to other antibiotics. It is administered at a dosage of 2 grams over a three-hour period every eight hours for 7–14 days [75]. However, no efficacy data in CF and paediatric patients are available, and the dosage in CF patients of any age has not been established. Compassionate use of the drug was conducted in 8 adult and paediatric patients with *A. xylosoxidans* infection who received 12 courses of the drug together, in 11 cases with other antibiotics effective against gram-negative rods [76]. The duration of cefiderocol administration varied from 2 days to 6 weeks. Resolution or improvement of disease symptoms after 30 days was observed in 11 cases, although in 3 patients, pretreatment evaluation revealed *in vitro* pathogen resistance. Unfortunately, microbiologic relapse was observed after 11 of 12 treatment courses, notably without emergence of resistance. Further evidence of the potential *in vivo* efficacy of cefiderocol in CF patients infected by Ac species is given by the case of a 10-year-old female treated with this antibiotic along with meropenem/vaborbactam and bacteriophage therapy [77]. Despite *in vitro* resistance of the pathogen to both cefiderocol and meropenem/vaborbactam, the patient's lung function improved dramatically, and the pathogen was eradicated from respiratory secretions 8 and 16 weeks after completion of therapy [77]. Finally, potential efficacy against Ac species infection is ascribed [78] to the meropenem-vaborbactam combination [79] and to eravacycline [80] for their *in vitro* activity against a number of gram-negative rods. However, for both preparations, no efficacy in CF and no dosage for CF patients are presently available.

6. Summary and perspective

Ac species, mainly *A. xylosoxidans*, are pathogens that have only recently been associated with CF. However, they have intrinsic characteristics that favour persistent lung colonization and several virulence factors and secretion systems that significantly interfere with respiratory cell survival. Finally, the bacteria can adhere to and penetrate respiratory cells and form biofilms that significantly reduce the host ability to combat them.

In many aspects, Ac species resemble *P. aeruginosa*. These findings and the evidence that Ac species are generally detected in patients with severe CF make them a significant component of CF respiratory microbiota. However, although it seems undebatable that Ac species detection is a marker of CF severity, the role of these pathogens as a cause of lung structure and function deterioration is not definitively established. Further studies are needed to solve this problem. Nonetheless, there is general agreement about the need for antibiotic therapy to eradicate these pathogens when they are detected in CF patients. Unfortunately, eradication is difficult, and no standard treatment is recommended by scientific societies. Antibiotics generally used in the treatment of gram-negative multiresistant strains are suggested. New possibilities are potentially offered by some recently developed drugs, such as cefiderocol, but further studies on the dosage, treatment duration and efficacy and safety of this new antibiotic in CF patients of different ages are urgently needed.

7. Author contributions

SE co-wrote the first draft of the manuscript; GP and VF performed the literature review and gave a substantial scientific contribution. NP co-wrote the manuscript and gave a substantial scientific contribution. All the authors approved the final version of the manuscript.

8. Ethics approval and consent to participate

Not applicable.

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11. Conflict of interest

The authors declare no conflict of interest.

12. References

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