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REVIEW

Management of refractory *Pseudomonas aeruginosa* infection in cystic fibrosis

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Abstract: Cystic fibrosis (CF) is the most common life-limiting inherited disease in Caucasian populations. The main cause of death in CF patients is respiratory failure resulting from chronic pulmonary infection. *Pseudomonas aeruginosa* is the most prevalent organism in the airway colonization of CF patients, and its persistence in the airways has been related to greater morbidity with a more rapid deterioration in lung function. *P. aeruginosa* has enormous genetic and metabolic flexibility that allows it to adapt and persist within the airways of CF patients, and it has the ability to easily acquire antimicrobial resistance. For these reasons, the management of infections and chronic colonization by *P. aeruginosa* remains a challenge for physicians. This article reviews the current and future antibacterial chemotherapy options for respiratory pseudomonal infection in CF patients.

Keywords: cystic fibrosis, *Pseudomonas aeruginosa*, respiratory infection, antimicrobial treatment

Introduction

Cystic fibrosis (CF) is a multisystem disorder caused by mutations on the cystic transmembrane conductance regulator (CFTR) gene located on chromosome 7.[1] It is the most common life-limiting, autosomal recessively inherited disease in Caucasian populations. Although this is a multisystem disorder, pulmonary disease remains the leading cause of morbidity and mortality in patients with CF. The primary cause of death in these patients is respiratory failure resulting from chronic pulmonary infection.[2] Early infections in CF airways are most frequently caused by *Staphylococcus aureus* and *Haemophilus influenzae*, organisms that may be seen in other young children with chronic illnesses and in adults with non-CF bronchiectasis. Other organisms that are identified later in the course of CF airways disease include *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, fungi including *Aspergillus*, and nontuberculous mycobacteria. Nevertheless, CF airway is particularly susceptible to *Pseudomonas aeruginosa*, which is considered the most important pathogen in this chronic disease. The prevalence of *P. aeruginosa* infection increases as patients age, such that >70% of adults are chronically infected.[3] *P. aeruginosa* is extremely difficult to eradicate once established in the CF airway. This phenomenon is due to poor penetration of antibiotics into purulent airway secretions, native or acquired antibiotic resistance, CF-related defects in mucosal defenses, or biofilms produced by the bacteria, which interfere with phagocytic killing. Although chronic infection has been referred as 'airway colonization', the presence of these bacteria is not benign. Epidemiologic studies show that chronic infection with *P. aeruginosa* is

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an independent risk factor for accelerated loss of pulmonary function and decreased survival.[4,5]

The quality of life and life expectancy of CF patients have improved considerably as a result of the control of bronchopulmonary bacterial colonization and exacerbations.[6] Nevertheless, because of the lack of scientific evidence, these issues remain a challenge for physicians.

This article reviews the current and future antibacterial chemotherapy options for respiratory pseudomonal infection in CF patients.

Epidemiology and pathogenesis of *P. aeruginosa*

P. aeruginosa is a usually noncapsulate, nonsporing, and nonfermenting Gram-negative bacillus that is common in the environment, especially in water. The ability of *P. aeruginosa* to persist and multiply in moist environments (soil detritus and equipment such as humidifiers in hospital wards, urinary catheters, bathroom sinks, and kitchens) is of particular importance in crossinfection.[7]

Currently, *P. aeruginosa* is a pathogen of great relevance in infectious disease for different reasons: *a*) reservoirs for infection can develop, especially in intensive care units, often associated with water in sinks or respiratory equipment; *b*) the microorganism displays a predilection for infecting immunocompromised hosts (including burn patients) whose proportion is increasing in our hospitals and society; *c*) it is the most serious pathogen in ventilator-associated pneumonia and one of the most common in other nosocomial infections; and *d*) there is an increase in occurrence of *P. aeruginosa* strains with resistance to multiple antibiotics.[8]

P. aeruginosa is the most common cause of respiratory failure in CF and is responsible for the death of the majority of these patients. Acquisition of *P. aeruginosa* begins early in childhood.[9]

It is believed that the bacterium is initially acquired from environmental sources, but patient-to-patient spread has also been described.[10,11] In patients with CF, prevalence of pseudomonal pneumonia ranges from 21% in those younger than 1 year to >80% in those older than 19 years. The increasing longevity of patients with CF has created a significant shift in the proportion of adult patients with CF; their proportion has increased fourfold, from 8% in 1969 to 33% in 1990.[12]

Impaired mucociliary clearance and bronchiectatic changes to the airways predispose patients with CF to lower respiratory tract bacterial colonization and recurrent infections, especially by *P. aeruginosa*.[13] *P. aeruginosa* has enormous genetic and metabolic flexibility that allows it to adapt to the milieu and persist within the airways of CF patients. The genotypes and phenotypes of the strains present in late stages of the disease differ substantially from those that initially colonize the lungs.[14] Initial isolates of this microorganism are often nonmucoid strains. As lung disease progresses, mutants with a mucoid phenotype owing to alginate overexpression are selected. Exopolysaccharide production is increased in response to the hypoxic environment of the mucus that covers the airway surface and contributes to highly structured biofilm formation.[15] Alginate protects *P. aeruginosa* from being killed by immune cells because it provides a physical barrier for the bacteria and it scavenges free radicals released by neutrophils and macrophages.[16] These mucoid strains are associated with deterioration in cough scores, chest X-ray scores, and pulmonary function.[17] Deterioration in lung function is related to anatomical changes in the airways caused by enhanced and persistent inflammation. Patients with CF have an increased number of neutrophils and levels of IL-8 in bronchoalveolar lavage (BAL) fluid and reduced production of IL-10, an anti-inflammatory cytokine, as compared with non-CF patients. Accordingly, they have an abnormally intense and prolonged inflammatory response to infections and the products of this excessive inflammation, which include neutrophil elastase and DNA fragments from apoptotic neutrophils, contribute to anatomic damage.[6]

The genetic and metabolic flexibility of *P. aeruginosa* also contributes to its ability to develop antimicrobial resistance, making eradication of *P. aeruginosa* infection almost impossible. One of the major mechanisms of resistance to many antibiotics is the expression of multiple efflux pump systems.[18,19] In addition, *P. aeruginosa* has the ability to acquire antimicrobial resistance genes encoded in plasmids and transposons through horizontal transfer from other Gram-negative bacteria.[20]

Clinical assessment of pulmonary health status

Routine imaging and laboratory evaluations are critical to assessing pulmonary status in CF patients. These studies are used to monitor disease progression and response to therapeutic interventions and evaluate exacerbations.

Chest X-rays are helpful for defining disease progression (detection of hyperinflation with flattened diaphragms, retrosternal lucency, nodular opacities due to mucus plugging, and cystic changes due to bronchiectasis). Chest X-ray scores

have been developed for assessing disease progression,[21,22] but have never been used widely in clinical practice.[6]

High-resolution computerized tomography (HRCT) is more sensitive and specific than chest radiographs in identifying changes in early CF lung disease (airway wall thickening, gas trapping) and is particularly useful in identifying localized areas of bronchiectasis and parenchymal abnormalities.[23] Accordingly, HRCT is being used to document localized disease and respond to antibiotic therapy during acute exacerbations.[24] The cost and radiation exposure are some of the reasons that explain the lack of consensus guidelines for use of HRCT in CF care.[25]

The main measure of pulmonary status in individuals with CF is pulmonary function testing with spirometry or plethysmography. Lung function measurements are useful in documenting stability or progression of airway obstruction and air trapping. These tests are also useful to detect acute changes associated with pulmonary exacerbations and response to therapy.[6] The earliest spirometric evidence of obstructive disease is a decrease in expiratory flows at low volumes such as forced expiratory flow between 25% and 75%, while the most widely used parameter to evaluate lung status is forced expiratory volume in 1 second (FEV_1) because of the universal accessibility of spirometric equipment, standardized criteria for performance, availability of reference values, and reproducibility.[26,27]

In daily practice, FEV_1 has two important functions: 1) it is the primary marker for disease progression identified in numerous epidemiologic studies to predict decline in health status and mortality[28] and 2) it is the primary outcome measure used for defining clinical efficacy for therapeutic modalities in CF.[29]

Microbiological assessment of *P. aeruginosa*

Microbiological studies are mostly performed using sputum samples. However, collecting this specimen may be difficult in the younger patients. Oropharyngeal cultures have been well studied in this situation but their value is inferior to that of sputum because of their lower sensitivity.[30]

BAL is a more sensitive measure for diagnosing infection, and it is also more invasive. This test should be reserved for assessing patients unresponsive to antimicrobial therapy or those with progressive disease.[31] Hypertonic saline induction of sputum has been reported to be a good surrogate for lower airway sampling in both adult and older pediatric patients with CF.[32]

In patients with an early diagnosis of CF, it is essential to undertake continuous microbiological monitoring to detect incipient colonization by *P. aeruginosa*. In this stage, optimal frequency for performing sputum cultures is controversial. A monthly, or at least trimonthly, culture is advisable for patients without evidence of *P. aeruginosa* colonization in order to detect the initial isolation and initiate early treatment. From other patients, cultures should be taken whenever exacerbations present or, at least, every 2–3 months in periods with clinical stability.[33,34]

All *P. aeruginosa* morphotypes isolated in the culture should be tested for susceptibility to antimicrobial agents. There is consensus that incubation of susceptibility tests should be for at least 24 h to facilitate growth of mucoid and small-colony variants. The precise method to evaluate this issue remains controversial but it should permit calculation of the MIC.[35,36]

Interaction patterns of *P. aeruginosa* with lungs: colonization versus infection

'Colonization' refers to bacterial development on a surface without harmful effects while 'infection' indicates a pathogenic effect resulting from microbial invasion of the tissues.[5]

In CF patients, pulmonary infections are associated with symptoms and clinical signs of respiratory illness: increased cough, increased sputum production, decreased exercise tolerance or increased dyspnea with exertion, increased fatigue, decreased appetite, increased respiratory rate or dyspnea at rest, change in sputum appearance, fever, and increased nasal congestion or drainage. These clinical situations tend to correspond to clinical respiratory exacerbations of a chronic bacterial colonization.[37]

Classically, in CF patients the term 'colonization' has been used to describe a clinical situation without symptoms or signs consistent with pulmonary infection but with persistence of the same microorganisms in successive sputum cultures. In case of *P. aeruginosa*, its persistence in the airways has been related to greater morbidity with a more rapid deterioration in lung function.[4] For this reason, it could be more accurate to refer to this situation in terms of 'pathogenic colonization' or 'chronic infection'.[34]

Different microbiological patterns and criteria in pulmonary *P. aeruginosa* colonization/infection in CF patients are summarized in Table 1. This classification is clinically important because each situation should be addressed differentially from the therapeutic viewpoint.

Table 1 Microbiological patterns and criteria in pulmonary *Pseudomonas aeruginosa* colonization/infection in cystic fibrosis patients

Infection/colonization	Definition	Microbiological criteria	Comments
I. Initial colonization (first colonization event or pioneer colonization)	Detection of the first positive *P. aeruginosa* culture in the bronchial tree. No clinical symptoms	First positive *P. aeruginosa* culture	A positive culture following 1 year of negative cultures after finishing treatment is considered as a new initial colonization. The strains are usually nonmucoid colonies, with little diversity in morphotypes or antimicrobial susceptibilities
II. Sporadic or intermittent colonization	Intermittent presence of positive and negative *P. aeruginosa* cultures in consecutive samples after initial colonization. No signs of infection	Detection, within a period of 6 months of the initial colonization, of a positive *P. aeruginosa* culture among at least three cultures, with at least 1 month between each positive culture	Possible recovery of strains with mucoid colonies and other colonial morphotypes
III. Colonization with bronchopulmonary infection	Initial or sporadic colonization with presentation of clinical signs of infection	As for initial or sporadic colonization	In patients without microbiological specimens, the appearance or increase of antibodies in two successive blood samples, with at least 3 months between each sample, can be used as a diagnostic criterion
IV. Chronic colonization	Persistent positive *P. aeruginosa* cultures without new clinical signs of infection	Detection within a period of 6 months of a minimum of three positive *P. aeruginosa* cultures, with at least 1 month between the positive cultures	Usually produced by strains with mucoid colonies and other colonial morphotypes. This is the common pattern during advanced periods of the disease
V. Chronic bronchopulmonary infection (exacerbation)	Presentation of clinical signs of infection during the course of a chronic colonization	As for chronic colonization	In patients with microbiological specimens, an increase of antibodies in two successive blood samples can be used as a diagnostic criterion

Antimicrobial treatment in clinical practice

Special issues in CF pharmacokinetics

CF patients generally have a larger volume of distribution (V_d) for many antibiotics, including β-lactam agents and aminoglycosides, due to their lower fat stores and an increased ratio of lean body mass to total body mass compared with the non-CF population. Consequently, larger doses of antibacterial agents must be given to attain the same serum concentration as individuals with a larger adipose mass.[38,39] Enhanced total body clearance of antibiotics has also been observed within the CF population. Increased renal clearance, decreased protein binding, extrarenal elimination, and increased metabolism have been proposed as possible reasons for this increased clearance although the exact mechanism has not been determined. There are fewer pharmacokinetic deviations for fluoroquinolones; however, higher doses are typically needed for activity against CF pathogens.[38]

The increased V_d and enhanced clearance of antibiotics, combined with the difficulty of lung tissue penetration and *P. aeruginosa* antimicrobial resistance, make antibiotic dosing to get therapeutic drug concentrations a real challenge in CF patients. Aminoglycosides have been widely studied trying to optimize their therapeutic concentrations and minimize toxicity. The bactericidal efficacy of this antibiotic family is peak dependent (postdose drug concentration) while the main adverse effects such as nephrotoxicity are trough dependent (predose drug concentration).[40] Historically, aminoglycosides have been administered three times daily in CF patients with normal renal function; however, recent strategies have included once-daily dosing regimens in an effort to maximize peak and minimize trough concentrations.[41,42] A meta-analysis published in 2010 concluded that once and three times daily aminoglycoside antibiotics appear to be equally effective in the treatment of pulmonary exacerbations of CF patients with evidence of less nephrotoxicity in children in the once-daily regimen.[43]

Commonly used antimicrobial agents for *P. aeruginosa* infections are shown in Table 2.

Eradication strategies to prevent chronic *P. aeruginosa* infection

Active treatment of first isolation of *P. aeruginosa* is critical in order to delay or prevent chronic infection state and its clinical consequences.[44–47] The authors of a recent meta-analysis[48] conclude that treating of early infection results in microbiological eradication of *P. aeruginosa* for several months. There is insufficient evidence to state which antibiotics strategy should be used for the eradication of early *P. aeruginosa* infection because of the enormous heterogeneity in regimens administered by clinicians from different CF specialized centers.[45,49,50] These regimens most often include the combination of oral fluoroquinolones and/or intravenous antipseudomonal agents with a prolonged course of inhaled tobramycin or colistin. In our setting, stable patients (without respiratory symptoms) usually receive oral ciprofloxacin (30–40 mg/kg/day) divided into two doses (maximum 2 g/day) for 3–4 weeks combined with inhaled tobramycin or colistin. If sputum culture is negative 1 month after the start of treatment, the inhaled therapy is maintained for at least 6 months to avoid early recurrence; whereas, if culture is positive, the treatment cycle is repeated. If the sputum collected at the end of the second cycle is still positive, the patient is considered chronically colonized.[34] For positive *P. aeruginosa* cultures, an antibiogram should be performed and the antimicrobial therapy should be adapted accordingly. Despite the high prevalence of susceptibility to antipseudomonal antibiotics found in *P. aeruginosa* associated with initial infections, an antibiogram should also be performed in this situation because susceptibility in early isolates cannot be presumed.[51] The US multicenter Early Pseudomonas Infection Control (EPIC) study is currently in process. This investigation is evaluating different strategies for early *P. aeruginosa* eradication and observing the natural history of its acquisition in early childhood.

Maintenance after development of chronic *P. aeruginosa* infection

Both oral and inhaled antibiotics offer potential benefits to patients with chronic respiratory *P. aeruginosa* infection. A large placebo-controlled trial assessing the use of inhaled tobramycin given twice daily on an alternating month basis for 6 months was published in 1999 and shows clear benefit to the use of this regimen as a chronic maintenance therapy for patients colonized with *P. aeruginosa*.[29] Pulmonary function was improved and the need for hospitalization was decreased among patients in the inhaled therapy group compared with placebo. Long-term follow-up of patients using inhaled tobramycin has demonstrated efficacy and no significant side effects.[52] In recently published US guidelines, the chronic use of inhaled tobramycin is recommended for patients aged 6 years and older with *P. aeruginosa* persistently present in cultures of the airways in order to improve lung function and reduce exacerbations.[53]

Nebulized colistin is also commonly used as chronic maintenance treatment for *P. aeruginosa* colonization. One short-term trial of 1 month, with 115 patients included,

Table 2 Antibiotics for the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis

Antibiotic	Pediatric dose	Adult dose
Oral ciprofloxacin	10–20 mg/kg twice a day	500–750 mg twice a day
Tobramycin via inhalation	300 mg by nebulizer, twice a day[a]	300 mg by nebulizer, twice a day
Colistin via inhalation	75–150 mg by nebulizer, twice a day[b]	75–150 mg by nebulizer, twice a day
Ciprofloxacin	10 mg/kg intravenously every 8–12 h	400 mg intravenously every 12 h
Ceftazidime	50–100 mg/kg intravenously every 8 h	2 g intravenously every 8 h
Cefepime	50 mg/kg intravenously every 8 h	2 g intravenously every 8 h
Piperacillin–tazobactam	90 mg/kg intravenously every 6 h	4.5 g intravenously every 6–8 h
Aztreonam	50 mg/kg intravenously every 8 h	2 g intravenously every 8 h
Imipenem	15–25 mg/kg intravenously every 6 h	500 mg to 1 g intravenously every 6 h
Meropenem	40 mg/kg intravenously every 8 h	1–2 g intravenously every 8 h
Doripenem	10–15 mg/kg intravenously every 8 h	500 mg intravenously every 8 h
Tobramycin	5–10 mg/kg intravenously every 24 h[c]	7 mg/kg intravenously every 24 h[c]
Amikacin	20–30 mg/kg intravenously every 24 h[d]	15–20 mg/kg intravenously every 24 h[d]
Colistin	1.5–2 mg/kg intravenously every 8 h[e]	80–160 mg intravenously every 8 h[f]

Notes: [a]In patients <6 years, inhaled tobramycin, 80 mg/12 h; [b]Dose expressed as milligrams of colistimethate; 1 mg of colistimethate = 12,500 IU. The recommended dose of 75–150 mg/12 h is approximately equal to 1–2 million IU, twice a day; [c]Dosage should be adjusted to serum trough concentration <1 μg/mL; [d]Dosage should be adjusted to serum trough concentration <4–5 μg/mL; [e]Dose expressed as milligrams of colistimethate for patients <60 kg. Pediatric dose: 18,000–24,000 IU/kg every 8 h; [f]Dose expressed as milligrams of colistimethate for patients ≥60 kg. Adults dose: 1–2 million IU every 8 h.

compared tobramycin and colistin and showed a trend toward greater improvement in FEV_1 in the tobramycin group.[54] However, the use of one agent over the other was not favored in a large meta-analysis.[55] In this meta-analysis, the incidence of antibiotic resistance with inhaled maintenance therapy was assessed and was of low-frequency occurrence. Nevertheless, patients with highly resistant pathogens detected in sputum cultures may still derive clinical benefits from aerosolized drugs like tobramycin.[56] This should be due to the pharmacodynamic benefits of inhaled antibiotics with high concentrations attained in the site of infection and low risk of systemic toxicity.[57] Despite this low risk of systemic toxicity, it has been found that after inhalation of aminoglycosides significant serum drug levels can appear.[58–60] This fact should be considered in patients with baseline renal failure or in patients receiving other nephrotoxic agents.

Other inhaled agents such as aztreonam, fluoroquinolones, and amikacin are in developmental stages and hold potential as alternative agents for chronic maintenance therapy.[61] Aztreonam lysine for inhalation solution has been studied in two phase III, randomized, placebo-controlled trials in CF population, and it has shown improvement in respiratory symptoms, pulmonary function, and sputum *P. aeruginosa* density in the treated patients.[62,63]

There is growing interest in evaluating combination therapies to combat *P. aeruginosa* biofilms in the airways of CF patients. Colistin–tobramycin combination has been assessed in biofilm models in vitro and in rat lungs, showing better results than in those cases receiving single antibiotics. In five CF patients, inhaled colistin–tobramycin was well tolerated and resulted in a mean decrease of log(10) cfu of *P. aeruginosa* per milliliter of sputum.[64]

Oral antipseudomonal antibiotics could be a comfortable alternative to nebulized therapy for maintenance of long-term treatment. Fluoroquinolones have several characteristics that have made them appealing for oral maintenance therapy: broad spectrum antibacterial activity with excellent bactericidal activity against most *P. aeruginosa* strains, excellent oral absorption, and bioavailability in airway secretions.[65] Despite ciprofloxacin monotherapy having demonstrated comparable results with intravenous drugs treating mild exacerbations, the emergence of fluoroquinolone-resistant *P. aeruginosa* in treatments for more than 3–4 weeks has been observed.[66] Thus, prolonged treatment with this antibiotics class is discouraged.[6]

Use of azithromycin, 250 or 500 mg three times weekly, has been recommended for patients with chronic *P. aeruginosa* colonization.[53,67] As a bacteriostatic effect of macrolides against *P. aeruginosa* has not been reported, it has been suggested that an immunomodulating activity is responsible for the observed improvement in CF patients.[68] This anti-inflammatory effect has been demonstrated in in vitro models and in mice.[69,70] A recently published meta-analysis demonstrated that the regular use of oral azithromycin shows a small, but significant, improvement in respiratory function at the 1- and 6-month points.[71] Some studies also suggest a decrease in the number of exacerbations,[67,72,73] and only one reported a significant increase in mild adverse events like nausea, diarrhea, and wheezing.[67]

Treatment of patients with exacerbations

The aim of exacerbations treatment is to restore the baseline lung function present before the onset of respiratory symptoms. In this situation, the antimicrobial therapy is targeted to decrease the bacterial inoculum in the sputum because the eradication of the pathogen is virtually impossible.[74,75] Moderate and severe exacerbations should be treated with intravenous agents while oral antibiotics (basically ciprofloxacin) are recommended for patients with mild respiratory worsening.[34,76]

The choice of empiric antimicrobial agents is usually based on finding two drugs with differing mechanisms of action which demonstrate in vitro efficacy on conventional drug susceptibility testing of previous sputum cultures and secondly, modifying these agents according to the susceptibility testing of current samples.

Common intravenous regimens generally include the use of an antipseudomonal β-lactam (piperacillin–tazobactam, ceftazidime, cefepime, meropenem, imipenem, or aztreonam), combined with an aminoglycoside (amikacin much more widely used than gentamicin or tobramycin). The standard approach to antibiotic treatment of exacerbations due to *P. aeruginosa* has been to use two antipseudomonal drugs to enhance activity and reduce selection of resistant organisms, but this combination therapy has not demonstrated a clear superiority over monotherapy.[77] Use of a single antibiotic could result in reduced toxicity as well as cost, and these are important issues for patients who will be treated multiple times throughout life.[78] In a large systematic review, the overall results showed that there was no significant difference between monotherapy and combination therapy in terms of clinical outcome measures, such as lung function and symptoms scores, or in terms of bacteriological outcomes.[79] However, there was considerable heterogeneity among the eight trials included in the review, and their methodological

quality was poor. Consequently, adequate meta-analyses for most outcome measures could not be performed.

Standard treatment courses for exacerbations generally last for 14–21 days, but there are no clear guidelines or evidence on the optimum duration. Shorter courses should improve quality of life and compliance, result in reduced incidence of drug reactions, and be less costly. However, this may not be sufficient to clear a chest infection and may result in an early recurrence of an exacerbation.[80] Treatment can be administered at the hospital setting or at home if clinically and socially possible. Domiciliary intravenous therapy is becoming more common as it reduces the number of hospital admissions, entails fewer investigations, reduces social disruptions, and provides to some patients a better quality of life.[81,82]

An important tool that should complement the antibiotic treatment in respiratory exacerbations is the airway clearance therapy by chest physiotherapy (postural drainage with chest percussion in several anatomic positions to favor gravitational clearance of secretions of all lobes of the lung).[6,83]

Management of infections due to multiple drug resistant *P. aeruginosa*

Drug resistance is an inevitable problem in CF-related infections linked to the inability to eradicate chronically infecting pathogens and the requirement for repeated courses of antimicrobials during pulmonary exacerbations. In *P. aeruginosa*, multiple drug resistance (MDR) is defined as resistance to all agents in two or more classes of standard antibiotics, and its prevalence has been reported at 9.6%–19.2% of isolates.[84,85] MDR *P. aeruginosa* has been associated with increased number of exacerbations, accelerated rate of lung function decline, and increased risk of death.[86]

When *P. aeruginosa* loses susceptibility to the antipseudomonal antibiotics commonly used (fluoroquinolones and β-lactams), some old and new antibiotics must be considered.

Colistin, a molecule discovered more than 50 years ago, was discontinued because of a high incidence of nephrotoxicity.[87] This drug has received renewed interest because of its mode of action in disrupting the cytoplasmic membrane of Gram-negative bacteria.[88] This mechanism protects colistin from crossresistance from other antipseudomonal agents and is unlikely to lead to a rapid selection of new resistance.[89] The drug displays a concentration-dependent bactericidal activity[90] and has recently been reintroduced for the management of pulmonary infections in CF patients, either by intravenous route or in the form of an aerosol, with lower rates of toxicity than reported previously.[91,92]

Doripenem is a recently introduced carbapenem that offers potentially enhanced anti-Gram-negative activity relative to previously available drugs of this class but does not expand its spectrum of activity.[93] The MIC_{90} of doripenem is generally two-fold to four-fold lower than the corresponding values for meropenem and imipenem and, talking about MDR *P. aeruginosa* strains, this carbapenem remains active against 32% of CF isolates nonsusceptible to imipenem and 8.5% of isolates nonsusceptible to meropenem.[94] As other β-lactams, the pharmacodynamic parameter predictive of in vivo efficacy of doripenem is a percentage of the time over required MIC (%TMIC) (with 30% generally considered bacteriostatic and ≥50% considered bactericidal).[95] In modeling studies, using doripenem 500 mg infused over 1 h, %TMIC was 45% for a target of 2 mg/L, but when the infusion was extended to 4 h, this index increased to 68%.[96] Using 1 g of doripenem infused over 4 h, %TMIC increased to 81%. According to these results, because of its good tolerability and the absence of significant drug interactions,[97] this strategy using high doses and extended infusions of doripenem should be assessed in upcoming clinical trials.

Ceftobiprole is a new broad-spectrum cephalosporin with activity against most Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*, and similar Gram-negative spectrum to that of cefepime, including *P. aeruginosa*. It is not active against ceftazidime-/cefepime-resistant *P. aeurginosa*, so it does not provide benefits for treating MDR pathogens.[98]

There are methods of testing the susceptibility of bacteria to combinations of antibiotics. Combination antimicrobial susceptibility testing assesses the efficacy of drug combinations including two or three antibiotics in vitro and can often demonstrate antimicrobial efficacy against bacterial isolates even when individual antibiotics have little or no effect. Therefore, choosing antibiotics based on this synergy testing could potentially improve response to treatment in CF patients with acute exacerbation. There is only one randomized controlled trial comparing this strategy with conventional procedures, and its data did not provide evidence that combination susceptibility testing was superior to routine testing.[99,100]

Future therapies

Most upcoming antimicrobial drugs are new derivatives of existing families with similar mode of action. Therefore, they probably will not solve the problem of emerging multiresistant pathogens. Alternative antimicrobial approaches are gaining more interest to address this problem. Regarding

prophylactic measures, there have been many approaches in the development of vaccines for the prevention of *P. aeruginosa* infection, but early trials produced disappointing results.[101] However, a study showed that regular vaccination for a period of 10 years with a polyvalent conjugate vaccine reduced the incidence of chronic infection with *P. aeruginosa* and was associated with better preservation of lung function, particularly in older patients.[102] With current information, vaccines against *P. aeruginosa* cannot be recommended according to a recently published review,[103] so further investigations are required.

The main defense mechanisms against Gram-negative bacterial infections are complement-activated killing and complement-mediated opsonophagocytosis. Polysaccharides such as lipopolysaccharides are T cell–independent antigens that trigger the innate immune system via the stimulation of pattern recognition receptors (eg, Toll-like receptor 4). Antibodies induced in response to them are mostly of the immunoglobulin M (IgM) isotype. IgM antibodies have several favorable properties that support their use as therapeutic tools: their pentameric form provides 10 antigen binding sites, they bind antigens with high avidity, and IgM antibodies are very effective complement activators.[104]

Combined treatment with IgM monoclonal antibodies (MAbs) and antibiotics could lead to a more rapid resolution of infections, resulting in shorter stays in intensive care units as well as reductions of morbidity, mortality, and health care costs. Human-obtained MAb against *P. aeruginosa* was assessed in a murine burn wound sepsis model, where full protection of animals against lethal challenges with *P. aeruginosa* was achieved at very low doses. Also, an acute lung infection model using mice showed protection against local respiratory infections.

A study demonstrated the safety of this IgM MAb in healthy volunteers,[105] and these results warrant further testing of this strategy in infected patients in order to confirm the therapeutic potential of this compound.

Phage therapy is the therapeutic use of bacteriophages to treat pathogenic bacterial infections. Bacteriophages are viruses which specifically and uniquely seek out and destroy bacteria. They do not attack mammalian cells and exist as partners in microbiological ecosystems in the human body and in the environment. Although phage therapy has been known for over 90 years and in spite of the continued use of this technique in eastern Europe,[106] it has attracted worldwide renewed interest as an alternative or complement to conventional antibiotic therapy due to emergence of multidrug-resistant pathogens. This approach has demonstrated its efficacy in mouse burn wound *P. aeruginosa* infection model[107] and in mice gut-derived *P. aeruginosa* sepsis model.[108] The first controlled clinical trial of a therapeutic bacteriophage preparation in humans showed efficacy and safety in chronic otitis due to multidrug-resistant *P. aeruginosa*.[109]

This form of biological therapy has considerable promise, and it should be the subject of for further investigations.

Finally, therapies directed against virulence factors of *P. aeruginosa* (biofilm formation, quorum sensing, flagella, or type III secretion) have been the focus on much recent investigation. These promising translational strategies may lead to the development of adjunctive therapies capable of improving outcomes.[110]

Disclosure

The authors have no financial interest in this article.

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