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Published in:
Expert Opinion on Drug Metabolism & Toxicology

DOI:
10.1080/17425255.2021.1836157

Publication date:
2021

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Expert Opinion on Drug Metabolism & Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iemt20

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To cite this article: Anne M. Akkerman-Nijland , Onno W. Akkerman , Floris Grasmeijer , Paul Hagedoorn , Henderik. W. Frijlink , Bart. L. Rottier , Gerard. H. Koppelman & Daniel. J. Touw (2021) The pharmacokinetics of antibiotics in cystic fibrosis, Expert Opinion on Drug Metabolism & Toxicology, 17:1, 53-68, DOI: 10.1080/17425255.2021.1836157

To link to this article: https://doi.org/10.1080/17425255.2021.1836157

Published online: 29 Dec 2020.

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
2021, VOL. 17, NO. 1, 53–68
https://doi.org/10.1080/17425255.2021.1836157

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REVIEW

The pharmacokinetics of antibiotics in cystic fibrosis

Anne M. Akkerman-Nijland[a,b], Onno W. Akkerman[c], Floris Grasmeijer[d,e], Paul Hagedoorn[e], Henderik. W. Frijlink[e], Bart. L. Rottier[a,b], Gerard. H. Koppelman[a,b] and Daniel. J. Touw[b,f]

[a]Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [b]Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [c]Department of Pulmonary Diseases and Tuberculosis, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [d]Department of Pharmacy, PureIMS B.V, Roden, The Netherlands; [e]Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands; [f]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

ABSTRACT

Introduction: Dosing of antibiotics in people with cystic fibrosis (CF) is challenging, due to altered pharmacokinetics, difficulty of lung tissue penetration, and increasing presence of antimicrobial resistance.

Areas covered: The purpose of this work is to critically review original data as well as previous reviews and guidelines on pharmacokinetics of systemic and inhaled antibiotics in CF, with the aim to propose strategies for optimization of antibacterial therapy in both children and adults with CF.

Expert opinion: For systemic antibiotics, absorption is comparable in CF patients and non-CF controls. The volume of distribution (Vd) of most antibiotics is similar between people with CF with normal body composition and healthy individuals. However, there are a few exceptions, like cefotiam and tobramycin. Many antibiotic class-dependent changes in drug metabolism and excretion are reported, with an increased total body clearance for ß-lactam antibiotics, aminoglycosides, fluoroquinolones, and trimethoprim. We, therefore, recommend following class-specific guidelines for CF, mostly resulting in higher dosages per kg bodyweight in CF compared to non-CF controls. Higher local antibiotic concentrations in the airways can be obtained by inhalation therapy, with which eradication of bacteria may be achieved while minimizing systemic exposure and risk of toxicity.

ARTICLE HISTORY
Received 30 June 2020
Accepted 7 October 2020

KEYWORDS
Antibiotics; cystic fibrosis; drug disposition; pharmacodynamics; pharmacokinetics

1. Background

Cystic Fibrosis (CF) is the most common life-shortening, autosomal recessive disease among Caucasian populations [1]. Mutations in the gene encoding the CF transmembrane conductance regulator (*CFTR)* protein result in abnormal ion transport across cell membranes causing abnormally increased viscous mucus. This abnormality affects a number of organs including the airways, intestine, pancreas, and reproductive tract, making it a multisystem disease. Pulmonary disease is the major source of morbidity and mortality. It results from a vicious cycle of airway mucus obstruction, inflammation, and infection, leading to progressive lung damage and ultimately respiratory failure [2–4].

Survival in CF has increased immensely over the past 80 years, with a predicted survival of 6 months around 1940 to currently a median age over 40 years. This is in large part related to an improved understanding of the vicious cycle of airway infection, inflammation, and progressive airway destruction with the subsequent development and optimization of treatment strategies to help control this cycle [5]. The way in which patients with CF become infected with these specific pathogens has not been fully elucidated yet. A multifactorial model has been proposed which combines processes like mucosal dehydration, impaired mucociliary clearance, hypertonicity of the airway surface liquid resulting in less effective antimicrobial peptide activity, luminal hypoxia, and dysregulation of defense function, all resulting in favorable niches for bacterial infection [6]. Antibiotic treatment is crucial to treat infection, for improving or maintaining lung function, improving quality of life and prolonging survival as infection and inflammation still lead to progressive lung function decline with morbidity and mortality [7]. In about a quarter of CF pulmonary exacerbations lung function will not return to baseline despite antibiotic therapy [8]. With a mean annual rate of pulmonary exacerbations around 2.9 [9] and a mean relative lung function decline in non-responders of 24% (SD 17%) [8], this highlights the importance of appropriate antibiotic therapy.

Pharmacokinetic (PK) and pharmacodynamic (PD) knowledge of antibiotics play an important role in maximizing clinical effect while minimizing toxicity. Subtherapeutic antibiotic concentrations may result in treatment failure, and, in addition, may be an important factor resulting in bacterial resistance. Knowledge of altered PK of antibiotics in CF patients is essential in the selection of optimal dosage regimens, and thereby for achieving therapeutic efficacy and maximizing clinical benefit. As PK and

CONTACT Daniel. J. Touw d.j.touw@umcg.nl Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen 9700 RB, The Netherlands

Article highlights

- Dosing of antibiotics in people with cystic fibrosis is challenging, due to altered pharmacokinetics (PK), difficulty of lung tissue penetration, and increasing presence of antimicrobial resistance.
- PK of antibiotics plays a pivotal role in maximizing clinical effect, while minimizing toxicity. Due to the altered PK in the CF population, optimizing antibiotic treatment using therapeutic drug monitoring (TDM) is of clinical relevance. So, knowledge about the pharmacodynamic part of the TDM, including the Minimum Inhibitory Concentrations (MIC) and the physicochemical properties of the antibiotics is important.
- In the past, for nearly all antibiotics an increased volume of distribution (V_d) was found in cystic fibrosis patients. Newer studies show that after accounting for body size and composition, V_d is rather similar between people with cystic fibrosis and healthy individuals for most antibiotics. However, there are a few exceptions, like an increased V_d for cefotiam and a higher V_d/kg for tobramycin in pediatric CF patients.
- For penicillins and most cephalosporins, a decreased plasma protein binding was described in cystic fibrosis patients, resulting in increased clearance rates. This requires higher dosing of these antibiotics or a switch to continuous infusion to optimize pharmacodynamics. Increased clearance rates were also found for aminoglycosides and trimethoprim, requiring higher dosing in patients with cystic fibrosis.
- A combination of antibiotics of different classes can be given at the same time to prevent the emergence of resistance and to achieve synergy, especially in the treatment of *Pseudomonas aeruginosa*.
- Higher local antibiotic concentrations in the airways can be obtained by inhalation therapy, with which eradication of bacteria may be achieved while minimizing systemic exposure and risk of toxicity.
- Optimizing pharmacokinetics by drug delivery to the lungs is complex and depends on several factors: the delivery device in combination with the physico-chemical properties of the drug itself, particle-related factors, and patients related factors.
- Studies have shown that central airway deposition of inhaled antibiotics is higher with increased bronchial obstruction and mucus plugging, and that peripheral, diseased parts of the lungs receive less inhaled antibiotics than healthy areas. Therefore, it might be necessary to treat patients with more advanced disease with higher doses to achieve sufficient drug concentrations in the entire lung, in particular in diseased parts of the lung.

This box summarizes key points contained in the article.

PD together influence dosing, benefit and adverse effects, and PD places emphasis on the relationships between drug concentration and effect, also knowledge of PD is necessary.

The purpose of this work is to critically review original data as well as previous reviews and guidelines on pharmacokinetics of systemic and inhaled antibiotics in CF, with the aim to propose strategies for optimization of antibacterial therapy in both children and adults with CF.

1.1. Antibiotic therapy in CF

1.1.1. Microbiology

Bacteria that commonly infect the lungs of patients with CF include *Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa* (*Pa*) and *Stenotrophomonas maltophilia* [10]. Different bacteria are encountered in different age groups. *Staphylococcus aureus* and *Haemophilus influenzae* are frequently encountered in children. The prevalence of *Pa* increases with age [11] and in Europe more than half of the adult CF patients have chronic pulmonary *Pa* infections [12]. Its presence is associated with accelerated lung tissue destruction and decline in lung function, ultimately leading to increased morbidity and mortality [13–15]. Early *Pa* infections usually have a low bacterial load, offering an opportunity for eradication [16]. Once chronic infection is established, *Pa* is virtually impossible to eradicate with currently employed strategies [17,18].

The prevalence and incidence of different bacterial strains vary significantly among countries. Analysis of data of CF patient registries also demonstrate that the prevalence of the CF pathogens has been changing over the past decades [18]. Patient registries in Europe show a decrease in prevalence of *Pa* from 2011 (33.3%) to 2016 (29.8%), with an increase in prevalence of *Staphylococcus aureus* (35% in 2011 to 38.3% in 2016) [19]. Compared to Europe, in the US a higher prevalence of *Staphylococcus aureus* is found (67.9% in 2011), *Pa* (46.4% in 2016) and *Non-Tuberculous Mycobacterium* (NTM; 12.6% in 2016 in the US versus 3.3% in Europe) [20]. NTM infection, especially *M. abscessus*, can also cause progressive inflammatory lung damage, a condition termed NTM pulmonary disease. Predominantly in the US, the prevalence of *methicillin-resistant Staphylococcus aureus* (MRSA) has been rapidly increasing from 2% in 2001 to 26.5% in 2014, after which the prevalence has plateaued [20]. Although information on MRSA is not part of the European CF Patient Registry, many European countries report prevalence rates between 3 and 13% [21]. The presence of MRSA in the respiratory tract of CF patients is associated with worse survival [22].

1.1.2. Purpose of antibiotic therapy

Antibiotic therapy is one of the cornerstones in the treatment of CF. Antibiotics are used for treating pulmonary exacerbations based on acute infections, for eradicating pathogens in otherwise asymptomatic CF patients, and for reducing the bacterial burden in chronically infected patients, as some pathogens cannot be eradicated once a chronic infection has been established.

Antibiotics can be administered via various routes of administration: intravenously, intramuscularly, orally, or by inhalation. The severity of the symptoms, condition of the patient and the susceptibility to antibiotics (depending on sensitivity of the micro-organism) determine the appropriate course of therapy.

1.1.3. Systemic or locally administered antibiotics

Traditionally, intravenous antibiotics are often considered to be the most effective form of antibiotic delivery. However, a Cochrane review published in 2015 did not report evidence to suggest that any route of antibiotic administration is superior to another in CF [23]. A combination of antibiotics of different classes can be given at the same time, both to prevent the emergence of resistance and to achieve synergy, especially in the treatment of *Pseudomonas aeruginosa* [24]. Advantages of oral antibiotics over the intravenous route are

that oral dosing is very practical, a lower drug cost, the absence of cannula-related infections, and that there is no need for health professionals or equipment as is the case with intravenous antibiotics.

When comparing systemic antibiotics and inhaled antibiotics, an advantage of the latter is that they facilitate high drug concentrations at the target site in the lung, while minimizing systemic exposure and risk for toxicity. Furthermore, antibiotics that historically could only be administered intravenously in the hospital setting can now be inhaled at home. Limited data are available to define an adequate length of therapy with antibiotics [25]. Generally, the length of treatment is determined by the resolution of symptoms in combination with return of lung function to its previous baseline or to a new plateau.

2. Systemic antibiotics in CF

2.1. Pharmacokinetic considerations in CF

PK describes the way medications are absorbed, distributed, metabolized, and eliminated. The PK of antibiotics has been reported to differ between people with and without CF [26,27]. Some studies show that these differences seem to become more pronounced as the illness progresses [28]. In Table 1, we summarize pharmacokinetic considerations in CF.

2.2. Absorption

Changes to the intestinal tract found in patients with CF can alter drug absorption. One of the changes of the gastrointestinal tract is the presence of an exceptionally thick mucus layer [29]. Other changes of the gastrointestinal tract found in CF patients are chronic inflammation, fat malabsorption, impaired intestinal bicarbonate secretion, as well as dysmotility with constipation and delayed gastric emptying [29]. Research shows that of the total CF population 38% has gastroparesis, mostly found in patients >18 years of age and in patients with diabetes [30]. Moreover, approximately 5–10% of CF patients develop cirrhosis during their first decade of life [31]. The presence of cirrhosis can cause lower plasma drug concentrations due to portal hypertensive gastropathy and impaired gastrointestinal motility, but more frequently leads to increased bioavailability due to a decreased first-pass effect [32]. Despite all these mechanisms oral bioavailability (the fraction of an administered drug that reaches the systemic circulation) seems largely unaffected. Finally, since CF encompasses polypharmacy, comedication can impair the absorption and decrease bioavailability. For example, co-administration of cations (as ferrous sulfate and a multivitamin-with-zinc) with fluoroquinolones causes impaired absorption [33,34].

There is only one study investigating the absorption of penicillins in CF patients [35]. This study evaluated the bioavailability of oral cloxacillin in 16 patients with CF and in 12 healthy controls. The authors found that bioavailability of cloxacillin was more variable in CF patients than in the control group (respectively mean±SD: 50.2 ± 26.2% and 38.4 ± 16.7%), but the mean bioavailability was not significantly different between both groups.

For fluoroquinolones, most studies showed that the time to reach maximum serum concentration (t_{max}) is longer in CF patients than in healthy controls, even though a comparable maximal serum concentration (c_{max}) is reached [36–38]. Most studies found no change in bioavailability between CF patients and healthy individuals for ciprofloxacin [33, 39–41]. One study even found a higher bioavailability of oral ciprofloxacin in CF patients than in healthy volunteers (bioavailability of 80% and 57%, respectively) [42]. The cause of this higher bioavailability is not known, but the healthy volunteers received a higher oral dose (mg/kg) than the patients with CF, whereby a saturable absorption cannot be excluded. Also, in children, an equal bioavailability was found between children with CF and a control group [43]. Rubio reported a lower bioavailability in younger patients than older children (>13 years of age; 68% and 95%, respectively) [28], but this age effect was not observed in other studies [40,44].

Only one study determined the absorption of oral doxycycline in CF patients, and no difference in bioavailability was found between these patients and healthy volunteers [45]. The bioavailability of oral azithromycin was also found to be similar in patients with CF and in healthy individuals [46]. For sulfamethoxazole and trimethoprim, there are no data regarding bioavailability in CF patients.

2.3. (Volume of) distribution

The Volume of Distribution (V_d) is a concept relating the amount of drug in the body (dose) to the measured concentration of that drug in blood. It can be viewed as a property that arises from the relative affinity of a compound for other compartments or tissue versus plasma. Drugs that are highly water-soluble are generally confined intravascularly and have a small V_d, whereas lipophilic drugs or drugs with a high tissue binding generally have a large V_d.

A drug in blood exists in two forms: bound and unbound. Antibiotics bind reversibly to plasma proteins (serum albumin, alpha-1 acid glycoprotein, and lipoproteins). Decreased plasma protein binding for some antibiotics, especially multiple ß-lactam antibiotics [47], is observed in people with CF (mostly adults combined with a few adolescents), of which the precise mechanism is not completely understood [47,48]. Increased inflammatory processes that occur during acute pulmonary exacerbations may result in decreased production of albumin and, in addition, may alter albumin and protein binding of drugs [49]. Lower albumin and prealbumin concentrations have been reported for patients with CF than for healthy controls [50]. For drugs with a high degree of protein binding, the plasma proteins may become saturated with drug and any excess drug would be unbound, which can be then eliminated. Liver cirrhosis causes an enlarged V_d and reduced plasma protein binding resulting in a larger fraction of unbound drug. The pathophysiological changes for this are decreased levels of plasma proteins due to impaired synthesis in the liver, accumulation of endogenous substances

Table 1. Overview of changes in patients with Cystic Fibrosis (CF) compared to healthy individuals relevant for pharmacokinetics. Column 1 displays the aspect of the process of pharmacokinetics, column 2 represents the physiological change in CF versus healthy subjects, column 3 the effect of this physiological change for pharmacokinetics in general, column 4 the pharmacokinetic changes for the different classes of antibiotics used in CF, and column 5 the dose adjustment following this pharmacokinetic change.

	Changes in CF	Changes in PK	Changes in PK per antibiotic class	Implication for dosing per antibiotic class
Absorption	- Thicker mucus layer than normal - Chronic inflammation - Fat malabsorption - Impaired intestinal bicarbonate secretion - Dysmotility with constipation and delayed gastric emptying - Polypharmacy	- Altered extent of drug absorption - Decreased rate of absorption	- ß-lactam antibiotics: no significantly different mean bioavailability, although more variability - Aminoglycosides: not applicable as no oral administration possible - Fluoroquinolones: most studies show no significant difference in mean bioavailability, although t_{max} is longer - Other: no significant difference in bioavailability is found for doxycylin and azithromycin; no data on sulfamethoxazole and trimethoprim	A higher dosage is needed when bioavailability is reduced. As there are no significant differences in bioavailability for antibiotics, no dosage alterations are needed for this parameter.
Distribution	- Worse nutritional status, with a relatively high lean body mass - Decreased production of albumin and/or altered binding of drug due to inflammatory processes	- Larger V_d for some antibiotics - Decreased plasma protein binding	- ß-lactam antibiotics: for most penicillins no significant difference in V_d after scaling by body size/composition, only for cefotiam a 38% larger V_d is found - Aminoglycosides: most studies show no significant difference in V_d after scaling by body size/composition; large intersubject variability; V_d/kg for tobramycin significantly higher in pediatric patients; Tobramycin V_d correlates better with LBM than with actual body weight - Fluoroquinolones: no consensus, most studies report no significantly higher V_d - Other: no significant difference is found for doxycycline and vancomycin	When V_d is enlarged a higher loading dose is needed. For most antibiotics no adjustments are needed when the CF patient is not underweight. However, when the patient is underweight they require a larger dose per kg bodyweight. As for cefotiam a 38% larger V_d is found in CF, a 38% higher loading dose is required. Pediatric patients require a 20% higher mg/kg dose tobramycin.
Metabolism	- Possibly altered expression of metabolizing enzymes of transporters	- Decreased plasma protein binding - Increased metabolism	- ß-lactam antibiotics: only for penicillins that are metabolized (cloxacillin and dicloxacillin) a higher nonrenal clearance is found - Aminoglycosides: not applicable - Fluoroquinolones: fleroxacin is extensively metabolized with an increased nonrenal clearance - Other: increased metabolic clearance of sulfamethoxazole	A higher total body clearance demands a higher maintenance dose.
Elimination	- Decreased production of albumin and/or altered binding of drug due to inflammatory processes - Other mechanisms remain to be elucidated: proposed are increased tubular secretion, decreased tubular reabsorption, extrarenal elimination	- Increased elimination	- ß-lactam antibiotics: higher clearance for penicillins, ceftazidime and cefotiam; clearance rates of cefepime, imipenem and meropenem are similar, although a higher clearance for meropenem is found for CF children - Aminoglycosides: increased total body clearance - Fluoroquinolones: most studies show no differences in clearance rate, there seems to be however an age-related increase in drug clearance with children eliminating the drug faster - Other: no significant difference is found for clearance of vancomycin, however in children there seems to be an increased clearance as body weight increases; total plasma clearance of both sulfamethoxazole and trimethoprim is increased	A higher total body clearance demands a higher maintenance dose. The on average 13% higher clearance of ß-lactam antibiotics requires approximately 13% higher doses, although this may not be clinically relevant for less severe infections. Prolonged/continuous infusions of ß-lactam antibiotics are recommended. Therapeutic drug monitoring can be an option. For aminoglycosides therapeutic drug monitoring is required. No dose adjustments are required for the fluoroquinolones, nor for vancomycin.

displacing the binding sites of plasma proteins, and fluid retention [32].

Calculations of V_d for ß-lactam antibiotics are discordant between older and newer studies. Studies before 1990 found higher values for V_d in CF patients, as the V_d was reported for total body weight. In patients with low nutritional status lean body mass is relatively high, and since ß-lactam antibiotics and aminoglycosides are primarily distributed into lean tissue, this results in a larger V_d per kg bodyweight [26]. These data of the past may no longer represent CF patients today, as they currently have better nutritional status and higher body weights. More recent studies used body size and body composition (with body surface area or lean body mass) to compare CF patients and healthy volunteers. They found that in CF patients who were not underweight V_d for ß-lactam antibiotics was similar to that of non-CF patients [47,48]. Thus, in normal nourished CF patients, the dose per kg of bodyweight may be similar to healthy controls, whereas underweight CF patients may require a larger dose per kg of bodyweight. Bulitta presented a quantitative model explaining the observed PK differences of ß-lactam antibiotics between CF patients and healthy volunteers from studies over the past four decades [47]. They found that V_d was similar between subject groups after scaling by body size and composition. However, Shah studied the PK differences of cefotiam between patients with CF and healthy volunteers [48]. After accounting for differences in body size and body composition, CF patients still had a 38% larger V_d than healthy volunteers. A larger V_d means that a higher loading dose is necessary. When the total body clearance is increased as well, also a higher maintenance dose is needed.

For aminoglycosides, there is discordance when evaluating V_d between CF patients and healthy volunteers. Some studies, for example those performed by Kearns [51] and Kelly [52], found a higher V_d for gentamicin and tobramycin in CF than in the healthy population. As with the ß-lactam antibiotics, a larger V_d can be explained by a relative lack of adipose tissue as Kelly did not adjust for body size/composition. Most other studies, like studies by Autret [53], Mann [54] and Grenier [55] did not find significant differences of V_d between both groups with a comparable body composition. Many studies stress the large intersubject variability in PK parameters for aminoglycosides in patients with CF. Touw found that the mean V_d/kg for tobramycin was significantly higher in pediatric CF patients than in adult patients (0.363 L/kg versus 0.294 L/kg; $p < 0.01$) [56]. They implied that pediatric CF patients require on average a 20% higher tobramycin dose (mg/kg) to achieve the same target peak serum concentration. The same authors found that V_d was significantly larger with once-daily tobramycin compared to thrice daily in pediatric CF patients (V_d 0.40 l/kg ±0.09 for once daily versus V_d 0.35 l/kg ±0.04 for thrice daily, with $p < 0.001$), which would imply a relatively larger dose when using the once-daily regimen to achieve target peak levels.

Evaluating the fluoroquinolones, Pai [34] and Reed [36] did not find a significant difference in V_d of oral ciprofloxacin or levofloxacin between patients with CF and healthy individuals. However, one study reported a larger V_d for oral ciprofloxacin in adults with CF than in healthy controls [57], while another study found a smaller V_d compared with healthy controls [58]. For intravenous ciprofloxacin, Davis found a similar V_d for CF patients and healthy volunteers [57], while Christensson found a larger V_d in the CF population [42]. Christensson also found a higher absolute bioavailability for oral ciprofloxacin [42]. However, as the increased bioavailability is offset by increased clearance, the authors concluded that no dose adjustments were necessary.

For doxycycline and vancomycin, the V_d was found to be similar between CF patients and the healthy population [45,59]. Also, no difference in V_d of vancomycin was found between children with CF and non-CF children [60]. For sulfamethoxazole and trimethoprim, a smaller V_d for trimethoprim in patients with CF compared to healthy volunteers was found by Reed, probably resulting from their reduced body fat mass [61]. However, Hutabarat found no significant difference in V_d [62]. As Hutabarat studied intravenous trimethoprim, the difference found by Reed may be due to a difference in bioavailability as he studied oral trimethoprim. Thus, when accounting for body composition, Vd appeared to be comparable between CF patients and healthy controls.

2.4. Metabolism

CF patients are thought to have an altered expression of metabolizing enzymes or transporters [27]. Only the antibiotics that are metabolized are influenced, which include some penicillins, fluoroquinolones, trimethoprim, and sulfamethoxazole [26].

For penicillins that are metabolized, such as cloxacillin and dicloxacillin, the mean nonrenal clearance of cloxacillin was found to be 144% higher in patients with CF than in healthy controls [35].

For fleroxacin, a fluoroquinolone that is rapidly and completely absorbed and extensively metabolized, formation and elimination clearance of its metabolites (N-oxide fleroxacin and N-demethylfleroxacin) were higher in CF patients, up to 40–70% [63].

Sulphamethoxazole is cleared from the body primarily by metabolism (93% of the dose) and less by renal excretion (7%) [64]. A large proportion of the sulphamethoxazole is acetylated by the liver to N4-acetylsuplhamethoxazole. CF patients have increased N4-acetylation of sulphamethoxazole, resulting in increased total plasma clearance [61,62].

2.5. Elimination (clearance)

Within the CF population, an enhanced total body clearance of antibiotics has been observed, although the precise mechanisms remain to be elucidated and may be different for various drugs. Possible causes that have been proposed in the literature are increased renal clearance, increased glomerular filtration rate, decreased protein binding, increased tubular secretion, decreased tubular reabsorption, extrarenal

elimination, and increased metabolism. Currently, it is unclear what role renal CFTR expression has in the enhanced clearance.

For the penicillins and ceftazidime, a higher clearance rate is found in CF patients [26,65,66]. Clearance rates of cefepime and imipenem seem to be comparable between CF patients and healthy volunteers. For meropenem one study showed no difference in PK between CF patients and the healthy population [67], although Pettit found a higher clearance in children with CF compared to children without CF [68]. In the earlier mentioned study of Bulitta [47], their quantitative model showed higher unbound drug concentrations for highly protein bound ß-lactams (as dicloxacillin, cloxacillin, methicillin, aztreonam), with only slightly higher (average 13%, range 0–27%) clearance rates in patients with CF. Therefore, to achieve the same average unbound concentrations at steady state, approximately 13% higher doses are required in CF patients [47]. This may not be clinically significant for less-severe infections to warrant dose adjustment [47]. As an alternative, shorter dosing intervals or prolonged infusion (for example, 3 hours instead of 3 min) or continuous infusion may be used to achieve similar times of unbound ß-lactam concentrations above the minimal inhibitory concentration. A CF-population PK model for cefotiam developed by Shah, showed that besides having a higher V_d, CF patients also have an 11% higher clearance rate [48]. The model explained these PK differences by a higher unbound fraction of cefotiam in patients with CF than in healthy volunteers, with higher unbound fractions of 74.4% in female and 56.3% in male patients with CF compared to 54.5% in female healthy volunteers and 50% in male healthy volunteers.

Total body clearance of aminoglycosides was reported to be increased in CF patients [26,51,52,54,69]. Levy reported that although total body clearance was increased, renal clearance seems to be similar in patients with and without CF [69]. These authors speculated that a decrease in tubular reabsorption might be the cause. Touw found that the elimination rate of tobramycin was reduced with 30% in patients receiving tobramycin once daily compared to thrice daily [56]. One of the possible explanations is a circadian pharmacokinetic behavior, because most of the patients received the once-daily tobramycin before sleep.

Most studies do not show a difference in clearance rate of fluoroquinolones between CF patients and healthy individuals [39–41], though one study reports an enhanced total plasma clearance for ciprofloxacin [42]. Two PK studies of ciprofloxacin in children with CF suggested an age-related increase in drug clearance, with children eliminating the drug faster than adults [43,44].

Clearance of vancomycin is reported to be similar between adult CF patients and healthy volunteers [59]. A population PK analysis in 67 pediatric CF patients showed that body weight significantly influenced vancomycin clearance, with increasing clearance as body weight increases [60]. The total plasma clearance of both sulfamethoxazole and trimethoprim is increased in CF patients [61,62].

2.5.1. PK/PD considerations of systemic antibiotics in CF (*Figure 1*)

Antibiotics are generally categorized in three different PK/PD classes, namely time-dependent, concentration-dependent, and dependent on total drug exposure with the area under the curve (AUC).

ß-lactam antibiotics demonstrate primarily time-dependent bacterial killing. They are most efficacious when drug concentrations are 4-5-fold above the Minimum Inhibitory Concentration (MIC) of the infective micro-organism for a given percentage of the time (generally between 40–70% of the dosing interval depending on the drug). Due to their dependence on the time that the drug concentrations are above the MIC, the increased elimination of ß-lactam antibiotics is an important factor to consider. Ways to optimize ß-lactam PK/PD properties include utilizing more frequent dosing or prolonged infusions (with extended-infusions or continuous infusion). Several studies demonstrated in non-CF populations that prolonged infusions of ß-lactam antibiotics resulted in higher clinical improvement and lower mortality rates [70]. Bakker compared continuous infusion with intermittent dosing of ceftazidime in CF patients. They concluded that with continuous infusion the same effect is achieved with two-thirds of the dose compared to intermittent dosing [71]. In the same study, they also showed that continuous infusion made iv treatment at home feasible, safe, efficacious, and cost-effective. In the earlier mentioned study of Shah, it was found that prolonged and continuous infusions of cefotiam achieve eightfold higher PK/PD breakpoints than short-term infusions every 8 hours [48]. Hubert evaluated prolonged infusions of ceftazidime in CF patients and concluded that in general prolonged infusions are as efficient as bolus dosing, but that in patients with resistant isolates of Pseudomonas aeruginosa prolonged infusions give better results [72]. The same was reported by Pettit and Thompson [49,68]. They found that prolonged infusions of meropenem provided a higher probability of target attainment against Pa. Another option to increase the probability of achieving PD targets is the utilization of therapeutic drug monitoring (TDM) for ß-lactam antibiotics. Hong used TDM and reported that clearance rates of ß-lactam antibiotics increased >20% during the first week of treatment of an CF exacerbation, which led to a dose adjustment in about 50% of patients [73].

Aminoglycosides exhibit concentration-dependent killing against susceptible organisms. Consequently, the ratio of C_{max} to MIC (C_{max}:MIC) is a predictor of efficacy, but also the ratio of AUC to MIC (AUC:MIC) is important. Both PK indices take into account the increased clearance and potentially larger V_d, which both lead to lower peak concentrations. Therefore, higher doses are routinely given to patients with CF compared to non-CF patients. A disadvantage of the aminoglycosides is their potential nephrotoxicity and ototoxicity. Both are associated with elevated trough levels and sustained elevated peak levels [74]. Previously, aminoglycosides were given in multiple daily dosing, but there is substantial evidence that the administration of once-daily dosing is equally

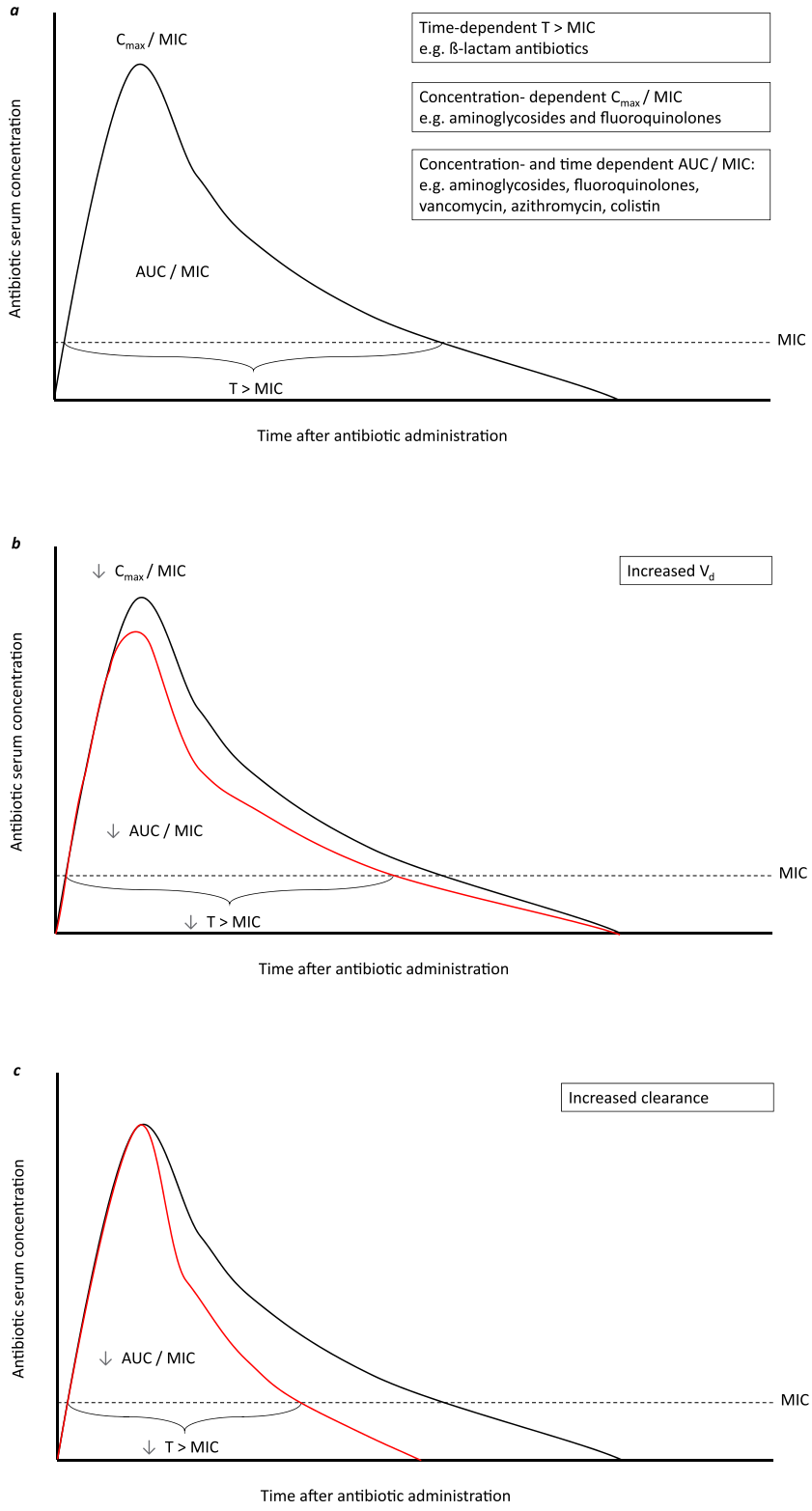

Figure 1. Illustration of the main PK/PD parameters that correlate with the efficacy of antibiotics (a), and PK/PD changes in increased volume of distribution (b) and increased renal clearance (c).

effective, while resulting in reduced nephrotoxicity (as there is a longer period of time in which there is little or no drug in de circulation) [75]. TDM of aminoglycosides is already widely used and especially important in the CF population.

The antibacterial activity of the fluoroquinolones increases with concentration. The AUC:MIC ratio is most predictive of microbiologic and clinical efficacy, with a ratio >30 for gram-positive and >125 for gram-negative organisms.

Some studies have suggested that the disease state of CF patients, having an acute pulmonary exacerbation or not, may influence the pharmacokinetics of several drugs [28,73]. Hong reported that clearance rates of ß-lactam antibiotics increased >20% during the first week of treatment of an CF exacerbation, which led to a dose adjustment in about 50% of patients [73]. Leeder evaluated the PK of ceftazidime in CF patients during acute pulmonary exacerbation and during an infection-free period [76]. They found no differences in PK except a 10% increased V_d during the infection-free period. Another study showed no influence of disease state on PK for cefepime [77].

In conclusion, whereas absorption and V_d for most antibiotics are comparable in CF patients with normal body composition compared to non-CF controls, many antibiotic class-dependent changes in drug metabolism and excretion were reported. We, therefore, recommend following class-specific guidelines for CF, mostly resulting in higher dosages per kg bodyweight in CF compared to non-CF controls [24,78,79].

3. Inhalation antibiotics in CF

3.1. When to prefer inhalation antibiotics?

The rationale for inhaled antibiotics is to achieve high drug concentrations at the target site in the lung, limiting systemic exposure and thereby minimizing systemic side effects. Compared to orally or parenterally administered drugs, inhaled drug doses may be considerably lower to achieve the same local effect. Because much higher local drug concentrations can be obtained, eradication of strains of microorganisms may be achieved that are considered resistant against the same drug given in the same dose via the systemic circulation, as resistance is often related to the drug concentration that can be achieved without toxicity [80]. Possible disadvantages of inhaled drugs are uncertainty about the drug dose at the target site, local side effects (as cough or less often bronchoconstriction and voice alteration) and variable systemic drug absorption [80].

The first report of inhaled antibiotic use in CF appeared in the literature in 1946 [81], but not until 1980–1990 the concept gained momentum and a series of trials were done assessing the use of inhaled antibiotics in the CF population. The development of inhaled antibiotics has primarily focused on antibiotics against Pa. Nowadays, inhalation antibiotics play a pivotal role in the management of CF, for eradication and suppression of chronic infection. The suppression of chronic infection aims to reduce the bacterial load in the lung which should reduce inflammation in the lung and thus reduce the rate of deterioration of lung function and frequency of exacerbations [82,83]. Another indication is eradication of Pa before evolving to a chronic form [16].

The most used inhaled antibiotics are tobramycin and colistin. Other inhalation antibiotics approved for use in CF patients by the European Medicines Agency are aztreonam, and levofloxacin.

3.2. Modes of delivery for inhalation antibiotics

A wide variety of devices is available for the delivery of inhaled antibiotics. Currently, inhaled antibiotics are either given via nebulization or dry powder inhalation. The main advantage of nebulization therapy is that it can be used by all different age groups as minimal coordination is needed and the drug can be inhaled while the patient is breathing tidally with no breath hold time required [84,85]. The main disadvantages of nebulizer therapy are [84]: (1) Nebulizer therapy is time-consuming, including both administration time and cleaning of the device. (2) Electricity is needed for the nebulizer, (3) the antibiotic in solution needs to be stored at cold temperature, (4) lung deposition as a percentage of the loading dose of the device is low with contamination of the surrounding environment, and (5) there is a risk of auto-re-infection (infection of the nebulizer leading to re-infection of the patient; only of interest for eradication therapy). Around the year 2000, inhalation of dry powder antibiotics became available. The main advantages of dry powder inhalers (DPI) are (1) DPIs have a short administration time, (2) they are small and portable, (3) some are disposable, so no maintenance is required and eliminating the risk of auto-re-infection, (4) with an efficient DPI a three to six-fold higher lung deposition compared to a nebulizer can be obtained [86]. The most important disadvantage of a DPI is that the lung deposition is highly dependent on the inhalation profile generated by the patient, which can have a high variation [87–89]. This is also why a careful instruction of the patient on inhalation technique is very important. A second disadvantage is that treatment with a DPI is not possible for children younger than 6 years of age.

3.2.1. Pharmacokinetics of inhalation antibiotics

Evaluation of the PK of drugs delivered through inhalation is much more complicated than that after administration of drugs by any other route. The effectiveness of aerosol therapy is dependent on how much of the drug will reach the target site in the lungs. The aim is to achieve the deposition of a sufficient fraction of inhaled particles at the target site, especially the peripheral airways as they cover approximately 95% of the total airway surface (Figures 2 and Figures 3). Particles deposited on the walls of the mouth and throat are swallowed or expectorated, so they will never reach their target site in the lungs.

After deposition in the lungs the antibiotic particles need to dissolve in the mucus and in the pulmonary epithelial lining fluid (ELF). Thereafter, the antibiotic has to diffuse toward the location of the bacteria. Here the drug must be retained long enough to produce its effect. So, key determinants of free drug concentration at the target site in the lungs are aerosol deposition, clearance from the lung (by mechanical clearance through coughing or swallowing, mucociliary clearance, uptake by alveolar macrophages and absorption in the systemic circulation), particle dissolution, diffusion rate, drug–tissue interactions, and absorption for systemic exposure.

Drug delivery to the lungs is complex and depends on several factors: the delivery device in combination with the

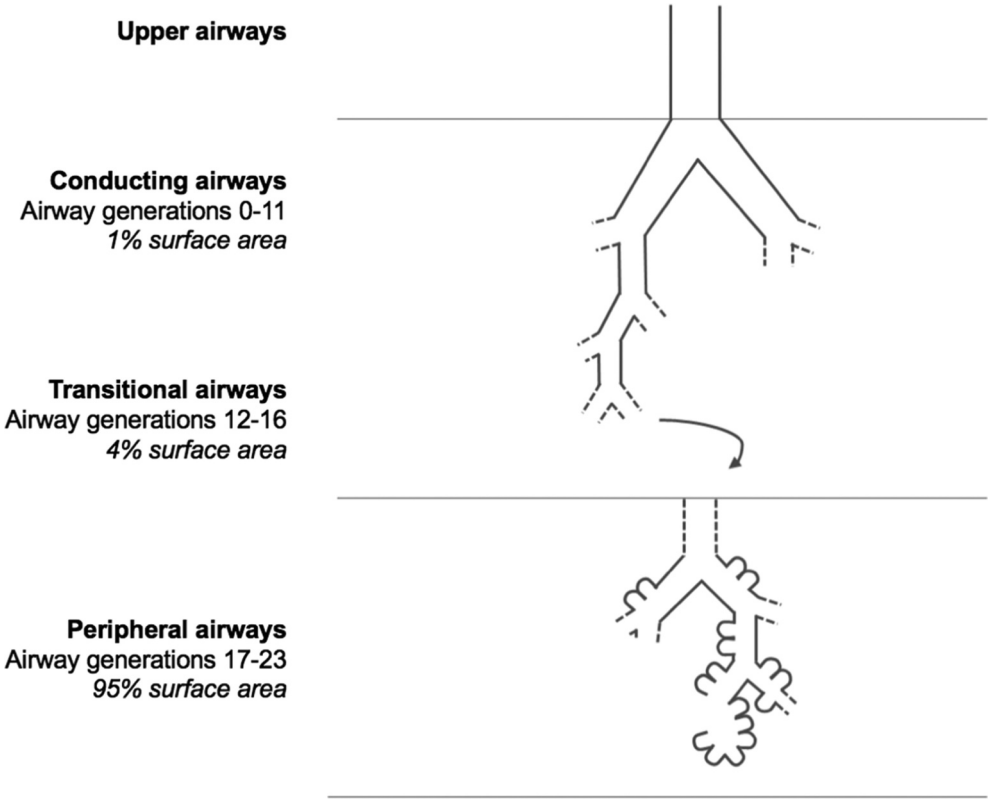

Figure 2. Anatomy of the lungs with increasing airway surface area.

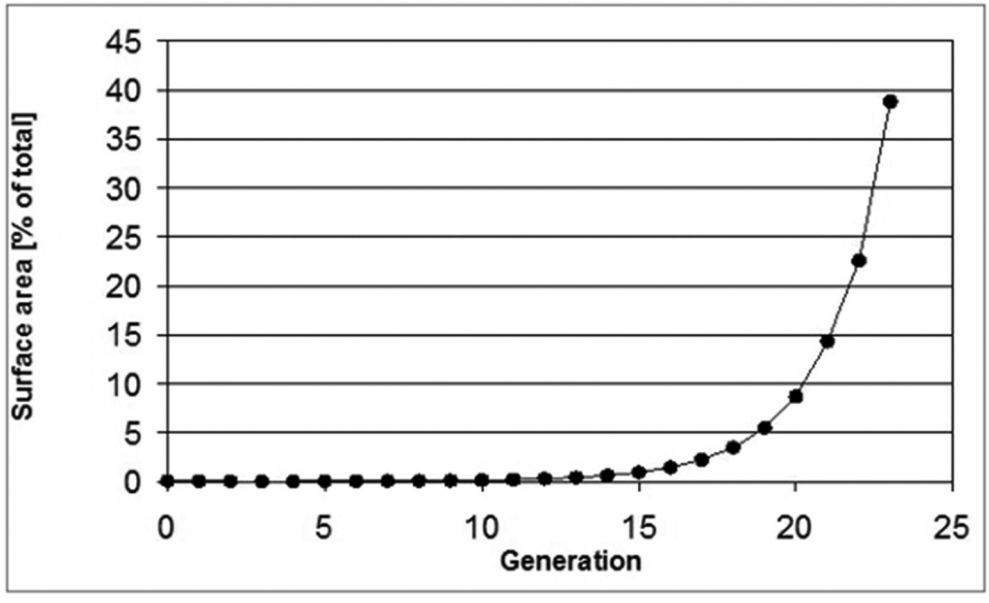

Figure 3. For each consecutive airway generation, concentrations will be lower as the total surface area of the airway surface increases exponentially.

physico-chemical properties of the drug itself, particle-related factors and patients related factors. These factors may contribute to variability in and uncertainty about the delivered dose (Figure 4).

The type of delivery device is of great influence on the lung deposition. Traditionally, jet nebulizers are used for the nebulization of antibiotics. These jet nebulizers may achieve a lung deposition of only 1–17% of the loading dose, measured as the percentage of dose absorbed systemically [90]. As jet nebulizers continuously generate aerosols during the respiratory cycle, aerosols are wasted during exhalation. In addition, after nebulization, there is a residue of around 1–1.5 ml. Some nebulizer systems are breath-actuated, in which the aerosol is only delivered from the nebulizer during

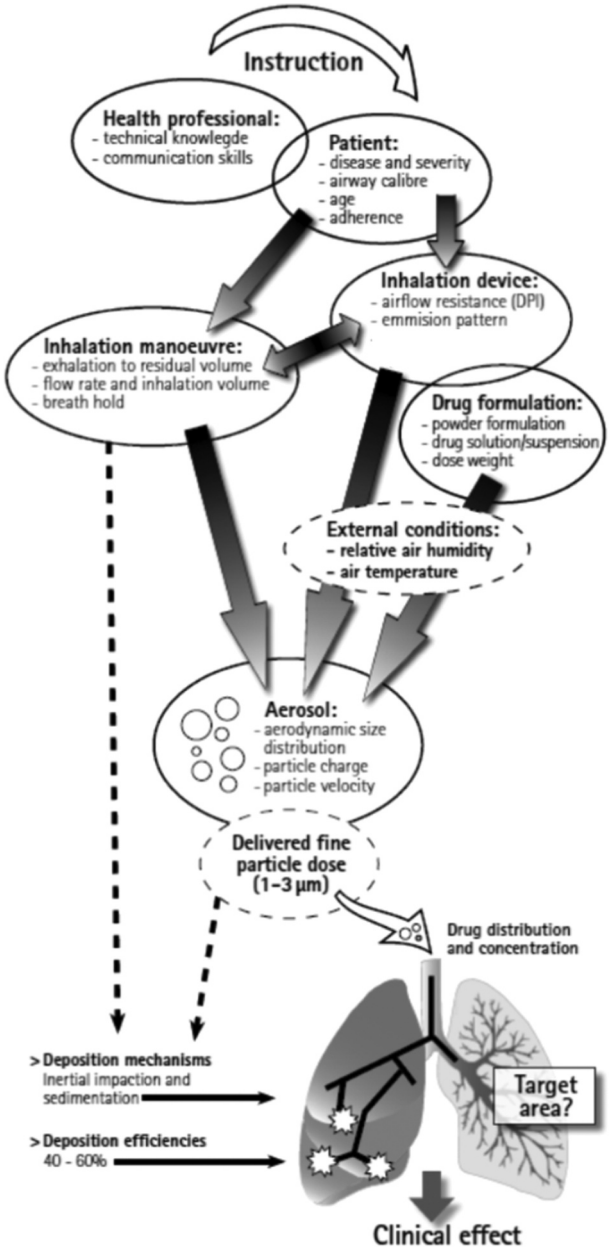

Figure 4. Interaction of the different contributing factors in drug delivery to the lungs (printed with permission by B.L. Rottier).

a pre-set fraction of the inspiration, and for some nebulizers the depth of the inhalation maneuver and flow rate can be set as well. This optimizes total lung deposition as wastage of medication during exhalation, which occurs with continuously delivering nebulizers, is terminated. In a comparison of a jet nebulizer with and without breath-actuation technique, Asmus found that a breath-actuated nebulizer delivered an estimated 22% more drug to the lungs using tobramycin urinary excretion [91].

Another type of nebulizer, the mesh nebulizer, is also thought to be more efficient than jet nebulizers, as there is virtually no loss of drug during exhalation and there is only a small residue of <0.3 ml after nebulization [84]. A Cochrane review compared deposition of tobramycin in CF patients using a jet nebulizer with a mesh nebulizer. The studies evaluating lung deposition through serum levels showed a lower lung deposition with the mesh nebulizers than with the jet nebulizers [92]. Also, among the different DPIs, lung deposition varies. Approximately 12–40% of the emitted dose is delivered to the lungs. In most DPIs 20–25% of the drug is being retained within the device [93], although there are DPIs with less inhaler retention around 7% [94].

Particle-related factors include size, shape, and density of the particles which influence their aerodynamic behavior. In general, aerosol particles smaller than 5 µm are thought to be respirable. The optimal particle size for deposition in the central airways is 3–5 µm and 1–3 µm for the peripheral airways, which is applicable at an average flow rate as deposition depends on the aerodynamic diameter in combination with the transport velocity. Particles of <1 µm are largely exhaled after inhalation [95].

Patient-related factors of lung deposition consist of the diameter of the airways, breathing pattern, inhalation maneuver, and the presence of abnormalities of the airways. Children have smaller airways and higher inspiratory airflows than adults, both facilitating central airway deposition [96]. The deposition of particles in the terminal airways is increased with an increase in tidal volume or breath-holding time [97]. A correct inhalation technique is the cornerstone for effective aerosol therapy. The quality of an inhalation maneuver depends on age, physical, and cognitive ability to perform a specific inhalation maneuver. With nebulization, young children use a face mask, decreasing the efficacy of lung deposition as the nasal route of inhalation is less efficient than oral inhalation. So, whenever the child is able to inhale through a mouthpiece this is the preferred method, as the efficiency of aerosol delivery can be doubled compared with inhalation by face mask [98]. In addition, young children can be uncooperative or be crying, thereby reducing lung deposition [99].

For all inhalation therapy, but particularly for DPI's, the inhalation maneuver is of utmost importance. For DPI's the energy for releasing and dispersing the powder into an aerosol with a proper aerodynamic particle size distribution is obtained from the inhaled air stream through the inhaler. The airflow rate has to exceed a certain threshold value for good drug dispersion, but also has a maximum threshold to prevent throat deposition. The airflow rate is dependent on the inhaler design. So, the optimal inhalation profile is dependent on the device [80]. Finally, aerosol deposition is also determined by the presence of structural abnormalities of the airways and/or mucus in the airways, which will be outlined below.

Unlike with systemic antimicrobials, there is no standard in the sampling and measurement of lung PK. In the literature serum drug levels after inhalation therapy are widely used as surrogate parameters for lung deposition when comparing different delivery devices and/or formulations. However, serum concentrations cannot be linked directly to target concentrations in the lung or in the epithelial lining fluid (ELF). So, for locally acting drugs, such as inhalation antibiotics, serum

concentrations are only a measure of the amount of drug that has passed through the lung tissue and is no longer available at the site of action. Measurement of drug concentrations in the lung is not routinely carried out because samples are very difficult to obtain, and it is nearly impossible to accurately estimate the concentration time profile in the lungs. Antibiotic levels measured in sputum after inhalation are highly variable and therefore not usable for pharmacokinetic investigations. Furthermore, it is highly unlikely that they are predictive for concentrations in the distal parts of the lungs as they overestimate the small airway concentration. In addition, pharmacokinetic methods lack the ability to identify dose deposition into different zones of the lungs.

3.2.2. Challenges of inhalation antibiotics in CF lungs

The lungs have developed multiple defense mechanisms directed to removing particles that would not normally reside in the airspaces. This presents an ongoing challenge for inhalation therapies. In CF lungs there are a few additional challenges.

3.2.3. Drug deposition in CF

Drug deposition differs between healthy individuals and patients with structural airway abnormalities. Several studies have shown that in CF central airway deposition is enhanced at the expense of alveolar deposition, most likely due to bronchial obstruction, mucus plugging and increased turbulent airflow, with also an inhomogeneous particle distribution in the airways [100–102]. As airflow is preferentially directed toward the healthier regions of the lungs, diseased areas will receive lower doses of drugs [103]. Bos made a patient-specific airway model with varying disease severity, for estimating aerosol concentrations of aztreonam lysine via nebulization in both central and small airways of patients with CF [104]. They demonstrated that inhaled antibiotic concentrations in the small airways are highly patient-specific. Deposition pattern in diseased lungs is more heterogeneous than in healthy lungs, with more severe lung disease having more central airway deposition [105,106]. They also observed that the upper lobes are more severely affected by structural disease relative to the other lobes. But even in patients with relatively little structural damage, the upper lobes received lower aztreonam lysine concentrations than the lower lobes. For the comparison between the deposition of DPI and nebulization, there are multiple studies looking at tobramycin inhalation. Evaluating deposition through gamma scintigraphy in healthy volunteers it was found that more drug was delivered to the lungs with DPI than with nebulization of tobramycin. A modeling study of Meerburg compared lung deposition of tobramycin nebulization with tobramycin dry powder, with varying inhalation maneuvers of the DPI, in patients with CF [107]. They found that small airway concentrations of nebulization were comparable with those of an instructed adequate slow inhalation with DPI. Uninstructed or inadequately fast inhalations with DPI tobramycin resulted in less tobramycin deposition in the small airways, although all inhalation maneuvers resulted in high enough estimated concentrations above the threshold for effective dose of 10x the MIC for Pa.

3.2.4. Mucus barrier and airway surface liquid

Mucus is a natural protective layer of epithelial cells in the trachea, bronchus and bronchioles and protects the body from the invasion of foreign substances as pathogens and toxins, through mucociliary clearance. CF mucus contains less water (around 90% versus 95% in healthy individuals) and more intact mucins such as DNA and actins, making it abnormally thick [108]. In CF patients, mucociliary clearance is reduced. The thick and tenacious sputum presents a significant challenge for effective inhalation therapy. Besides the fact that the viscous mucus forms sputum plugs interfering with drug deposition, it is also impeding antibiotic diffusion, delaying diffusion rate for both β-lactam antibiotics and aminoglycosides [109]. In addition, as antibiotics diffuse through the mucus layer to reach the site of the bacteria, the inhaled antibiotic may bind to and/or interact with various components in the sputum, limiting the amount of free drug available to act against the bacteria and with this decreasing efficacy [110]. Mucus binding applies specifically for the aminoglycosides, with tobramycin exhibiting the strongest binding to mucins and DNA (15–95%) [111], compared with amikacin (1–60%) [112] and gentamicin (mean 52%) [113]. Mucus binding has not been observed for β-lactam antibiotics. The difference in mucus binding results from the fact that aminoglycosides are positively charged and mucus plugs are mainly composed of negatively charged mucins and DNA, whereas β-lactam antibiotics are neutrally or negatively charged [114,115]. Conflicting results were described for the co-treatment of aminoglycosides with dornase alfa (recombinant human deoxyribonuclease), a mucolytic drug used to decrease the viscoelastic properties of CF sputum by cleaving extracellular DNA [115,116].

Furthermore, the thick and tenacious mucus creates areas of low oxygen tension [117]. Studies have shown that low oxygen tension reduces the efficacy of aminoglycosides and β-lactam antibiotics, as their uptake across the bacterial cell membrane depends on energy derived from aerobic metabolism [117,118]. In addition, low oxygen tension might facilitate the formation of biofilms for bacteria such as Pseudomonas aeruginosa [114]. Some studies have shown that colistin may be even more effective under anaerobic conditions [119,120].

3.2.5. Bacterial resistance

Bacteria found in the lungs of CF patients often develop antibiotic resistance, making it difficult to eradicate them. There are multiple barriers generated by the microorganism itself. Pa has the ability to change into mucoid strains that produce an alginate layer and form biofilms [121]. The alginate layer results in reduced diffusion of antibiotics, leading to reduced efficacy of the antibiotic. In addition, due to the alginate layer the bacteria can avoid phagocytosis. Biofilms are highly structured communities of bacterial cells encased within an extracellular matrix. Within the biofilm the oxygen

tension is low and there are few nutrients, slowing down the growth of the bacteria and with that reducing their susceptibility to some antibiotics [122]. The biofilm strategy is also used by Burkholderia and Stenotrophomonas species [123]. At present, there are no guidelines on adapting the dose in case of biofilms.

3.3. PK/PD considerations of inhaled antibiotics in CF

As stated above, there is no clear consensus on the site of action within the lungs that is most predictive of an optimal PK/PD response and which antibiotic concentrations are needed to achieve maximal killing throughout the lung. Lung disease in CF is thought to start in the small airways [124,125]. Bacteria are present throughout the lungs, with an inhomogeneous distribution in the airways of CF patients [84]. Antibiotic concentrations have to overcome the MIC values of the most resistant strains in the lung, also for the prevention of development of resistance. Thus, to obtain effective therapy the lowest drug concentration must be sufficiently high above the MIC values in all airways. It should be kept in mind that the total surface area of the airway surface increases exponentially with each consecutive airway generation. Unfortunately, a fall in concentration from the upper to lower parts of the lung is inevitable. On the basis of the involvement of the small airways in CF and the exponentially increase in surface area of the airways toward the alveoli, the peripheral airways should be targeted for inhaled antibiotics, so that concentrations sufficiently high above MIC are achieved there as well.

For inhalation therapy, different PK/PD targets may exist compared to systemic use with the same antibiotic. The currently approved and used MIC breakpoints for antibiotics are developed in part from plasma concentrations after systemic administration. However, inhalation therapy results in far higher lung concentrations than systemic use of the same antibiotic. This means that antibiotics administered through inhalation therapy may still achieve the required PK/PD index of efficacy even when the reported MIC values indicate that the targeted bacteria are resistant.

Typically used for inhalation are antibiotics that exhibit concentration-dependent bactericidal activity (e.g. aminoglycosides), since it is possible to obtain high concentrations in the lungs to maximize bacterial killing. Currently, chronic treatment of Pa with tobramycin or colistin exists of a twice-daily inhalation regimen. As aminoglycosides have a concentration-dependent effect, Bos evaluated the possibility of once-daily double-dosing [126]. In their modeling study, they compared local-inhaled tobramycin concentrations throughout the bronchial tree in CF patients after once- and twice-daily dosing. The once-daily double dose resulted in higher computed tobramycin concentrations in the small airways than the twice-daily dose. They concluded that the once-daily dosing regimen appears to be more suitable against more resistant Pa strains and is less prone to the inhibitory effects of sputum on tobramycin activity. However, for intravenous tobramycin therapy was reported that a once-daily dosing regimen was associated with a higher chance of antibiotic resistance development [127].

4. CF modulator therapy and consequences for antibiotics

An important advance in the treatment of CF of the past few years has been the development of CFTR modulators, which have the ability to enhance or even restore the functional expression of specific CF-causing mutations [128,129]. CFTR modulator therapy in general leads to an improvement in lung function, weight, quality of life, and a reduction in the number of exacerbations (the extent of which depends on which CFTR modulator therapy and which CF mutations the patient has). CFTR modulator therapy probably will become standard of care for CF patients [128]. Currently licensed modulators are ivacaftor, lumacaftor, tezacaftor, elexacaftor, and its combinations. With CFTR modulator therapy it is possible that the microbiology of the airways in the CF population will change substantially. Current data suggest that fewer infective problems will occur and perhaps infections will occur later in life when modulator therapy is started at a young age [130]. Singh found that CF patients who were receiving modulator therapy acquired fewer pathogens [131]. However, it is uncertain how long these microbial changes will last, as Hisert found that after starting with CFTR modulator therapy the bacterial density of *Pseudomonas aeruginosa* decreased but returned to pretreatment values after 2 years [132]. Such findings indicate that antibiotics will still be required to control disease symptoms in CF.

Co-administration of some antibiotics with CFTR modulators will result in drug interactions. As lumacaftor is a strong inducer of CYP3A, it may decrease the exposure of clarithromycin, erythromycin, and telithromycin, which may reduce their efficacy. It is not clear what the use of CFTR modulator therapy means for the PK of antibiotics as no data are reported yet. As weight is improved with modulator therapy, V_d will be similar to the non-CF population for most antibiotics. As the mechanisms for the increased renal clearance in CF patients are unclear, the effect that modulator therapy will have is unclear as well. For antibiotic inhalation therapy, the thick and tenacious sputum is one of the challenges in CF. As modulator therapy results in improved respiratory physiology, this will probably lead to more efficient drug deposition and probably in less mucus binding of antibiotics. There are no data available yet that report airway pH in response to CFTR modulator therapy. It might be that bicarbonate secretion is improved, resulting in a more alkaline environment, improving bacterial killing of antibiotics and thereby increasing efficacy.

5. Conclusion

Dosing of antibiotics in people with CF is challenging due to aspects related to altered pharmacokinetics and lung tissue penetration and the emergence of antimicrobial resistance. Knowledge of the altered PK of antibiotics in CF patients is

of great importance for selecting optimal dosage regimens, and thereby contributing to therapeutic efficacy and maximizing clinical benefit.

Up to now, studies on systemic antibiotics generally show no difference in bioavailability between the healthy and CF population. In the past, for nearly all antibiotics an increased V_d was found. Newer studies show that after accounting for body size and composition, V_d is rather similar between people with CF and healthy individuals for most antibiotics. However, there are exceptions, as with cefotiam for which V_d seems to be increased in CF patients, and there are discrepancies between studies, especially for aminoglycosides. For penicillins and some cephalosporins, a decreased protein binding is found in CF patients, resulting in increased clearance rates. Increased clearance rates are also known for aminoglycosides and for trimethoprim. Many PK studies in the CF population show large interindividual variability, further complicating antibiotic dosing. The strategy for children is similar to adults. Changing pharmacokinetics is a continuum from childhood to adulthood and pharmacodynamic principles remain the same.

Less information is available on PK of inhalation antibiotics. The major advantage of antibiotic inhalation therapy is that higher local drug concentrations can be obtained, with which eradication may be achieved of bacteria resistant to the same antibiotic given systemically, with less toxicity. More studies on pulmonary PK are needed to determine how deposition in the airways and the influence of lung disease affect drug concentrations at the target site in the lung and its efficacy.

6. Expert opinion

PK of antibiotics plays an important role in maximizing clinical effect while minimizing toxicity. This is even of more importance for CF patients due to their altered PK. So, optimizing antibiotic treatment using TDM is of clinical relevance for the CF population. As mentioned TDM uses the PK/PD principle. For this specific population, it is pivotal to know the PK alterations. Furthermore, optimizing treatment requires knowledge about the PD part of the TDM, including the MIC values and the physicochemical properties of the antibiotics. For example, options to optimize the PK/PD properties for systemically administered beta-lactams antibiotics can consist of the utilization of more frequent dosing or prolonged infusions (with extended- or continuous infusion), instead of the commonly used thrice daily dosing. Hong used TDM and reported that clearance rates of ß-lactam antibiotics increased >20% during the first week of treatment of a CF exacerbation, which led to a dose adjustment in about 50% of patients [73].

Inhalation therapy is used to achieve high concentrations of the antibiotics at the site of the infection. Current inhalation therapy consists of a 'one size fits all' method. Studies show that central airway deposition is enhanced as bronchial obstruction and mucus plugging increase and that diseased parts of the lungs receive less inhaled antibiotics than healthy areas. Therefore, it seems necessary to treat patients with more advanced disease with higher doses to achieve the PK/PD targets everywhere in the lungs. For children using nebulization with a face mask (which implies partially nasal inhalation and filtering), it has been shown that lung deposition is half that of oral inhalation. Therefore, children using this system need higher dosages for optimization of treatment.

Using the knowledge of the PK properties of antibiotics, inhalation therapy can be optimized by adjusting the frequency of administration for each antibiotic class. For the aminoglycosides with concentration-dependent killing and long post-antibiotic effect, once-daily dosing might result in more efficacious treatment than the current twice-daily dosing. On the other hand, to achieve an optimal response for inhaled ß-lactam antibiotics a higher frequency of administration would be needed. These alternative dosing regimens need to be investigated further. In addition, more studies on pulmonary PK properties of the different antibiotics are needed to determine how deposition in the airways and the influence of lung disease affect drug concentrations at the target site in the lung and with that its efficacy.

With the arrival of CFTR modulator therapy, which will become standard of care in western countries, it is possible that the PK in this population will change substantially and that the microbiology of the airways in the CF population changes as well. This will have an impact on antimicrobial pharmacotherapy in CF patients and it is, therefore, possible that antibiotic dosing regimens might require changes in the course of the next decade.

Funding

This paper was not funded.

Declaration of interest

P Hagedoorn and H Frijlink have patents WO2004/110538 and WO2015/187025 with royalties paid to the University of Groningen. GH Koppelman reports grants from the Lung Foundation of the Netherlands, TEVA the Netherlands, VERTEX, GlaxoSmithKline, Ubbo Emmius Foundation, TETRI foundation, outside of the submitted work. He has participated in advisory boards for GlaxoSmithKline and for PURE-IMS, outside of the submitted work. DJ Touw reports grants from ZONmw, Astellas, Chiesi, Tekke Huizinga Foundation and SKML, all outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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