



State of the art in cystic fibrosis pharmacology optimization of antimicrobials in the treatment of cystic fibrosis pulmonary exacerbations: III. Executive summary

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Abstract

Acute pulmonary exacerbations are complications of cystic fibrosis (CF) and are associated with increased morbidity and mortality. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Aspergillus fumigatus* are organisms that have been detected in the lungs of CF patients. The focus of this review is to provide an overview of the classes of antimicrobials used for MRSA and allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity reaction caused by *A. fumigatus*. The current anti-MRSA antibiotics and medications for ABPA dosing recommendations are discussed. This article also reviews the findings from the MRSA utilization surveys and the pharmacokinetic and pharmacodynamic differences between CF and non-CF patients. Antimethicillin *S. aureus* antibiotics include ceftaroline, clindamycin, fluoroquinolone derivatives (ciprofloxacin, levofloxacin), glycopeptide derivatives (telavancin, vancomycin), linezolid, rifampin, sulfamethoxazole/trimethoprim, and tetracycline derivatives (doxycycline, minocycline, tigecycline). Medications used for ABPA include corticosteroids, amphotericin B, azole antifungals (isavuconazole, itraconazole, posaconazole, voriconazole), and a monoclonal antibody, omalizumab.

KEYWORDS

ABPA, antibiotic therapy, cystic fibrosis, MRSA, pharmacology

1 | INTRODUCTION

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disorder that results from mutations to the cystic fibrosis transmembrane conductance regulator.¹ Patients with CF have periodic exacerbations of pulmonary infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Aspergillus fumigatus* are two organisms found in the lungs of CF patients.²⁻⁵ The prevalence of MRSA in patients with CF continues to increase.² Patients with CF are at an increased risk of pulmonary bacterial and fungal colonization due to impaired mucus clearance, local immunogenic dysfunction, and antibiotic use.⁶

This article serves as the executive summary to a series of articles on the management of MRSA and ABPA. The rationale for this

series is to (1) Summarize the literature on the dosing of anti-MRSA antibiotics and medications used for the treatment of ABPA; (2) discuss the need for higher dosing and/or improved dosing strategies as addressed in the pharmacokinetic (PK)/pharmacodynamic (PD) studies in CF; (3) establish appropriate antimicrobial dosing regimens; (4) identify areas of future study to assess the clinical benefit of antibiotic dosing optimization strategies in the patients with CF. The purpose of the executive summary is to provide an overview of the class of medications, the findings of anti-MRSA utilization surveys, the current antibiotic dosing recommendations from the United States and Europe, the PK/PD differences between CF and non-CF patients, and to provide an evidence-based summary of medication dosing for the treatment of MRSA and ABPA.

2 | METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

S. aureus is a common pathogen found in the airways of CF patients.² The prevalence of MRSA continues to increase in the CF population with CF care centers showing rates ranging from 0% to 50% in 2013.⁷ MRSA in the respiratory tract of CF patients has been associated with worse lung function, more rapid decline in lung function, decreased survival, and an increased risk of not recovering to baseline lung function after an exacerbation.²

3 | DESCRIPTION OF ANTI-MRSA ANTIBIOTICS

3.1 | Ceftaroline

Ceftaroline is a fifth-generation cephalosporin antibiotic with activity against *S. aureus*, both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) isolates.^{8,9} The PD measure of efficacy for ceftaroline is the time unbound plasma concentration exceeds the minimum inhibitory concentration ($T > MIC$).⁹

3.2 | Clindamycin

Clindamycin is a lincomycin derivative that has activity against Staphylococci species.⁸ Clindamycin is bacteriostatic or bactericidal depending upon the site of infection and drug concentrations.¹⁰ Clindamycin resistance to MRSA is high in patients with CF.^{11–14} The PD measure of efficacy for clindamycin is the area under the curve/minimum inhibitory concentration (AUC/MIC).¹⁵

4 | FLUOROQUINOLONE DERIVATIVES (CIPROFLOXACIN, LEVOFLOXACIN)

Ciprofloxacin and levofloxacin have activity against Gram-positive and -negative bacteria.^{8,16,17} Both ciprofloxacin and levofloxacin are bactericidal agents.^{16,17} The PD measure of efficacy for ciprofloxacin and levofloxacin is the AUC/MIC.¹⁸ Use of fluoroquinolones against MRSA is not routinely recommended due to the emergence of resistance.⁸

5 | GLYCOPEPTIDE DERIVATIVES (TELAVANCIN, VANCOMYCIN)

5.1 | Telavancin

Telavancin is a lipoglycopeptide that has activity against Gram-positive organisms including MSSA and MRSA.^{8,19} Telavancin is

bactericidal against Gram-positive organisms. The AUC/MIC is the PD measure of efficacy that correlates to *S. aureus*.¹⁹

5.2 | Vancomycin

Vancomycin is a glycopeptide antibiotic with bactericidal activity against aerobic and anaerobic Gram-positive organisms.^{8,20} The target PD measure of efficacy for vancomycin is AUC/MIC > 400 .²¹

5.3 | Linezolid

Linezolid is a member of the oxazolidinone class of antibiotics with activity against aerobic Gram-positive bacteria including MSSA and MRSA to which it is considered bacteriostatic against.^{8,22} The PD measure of efficacy for linezolid is AUC/MIC, with a target of over 80.²³

5.4 | Rifampin

Rifampin is a member of rifamycin antibiotics with potent antimicrobial activity against a variety of pathogens including MSSA and MRSA.^{8,24–26} Rifampin should be used in conjunction with other antibiotics due to the development of resistance if used as monotherapy. In patients without CF, the target PD measure of efficacy is an AUC/MIC > 271 .^{27,28}

5.5 | Sulfamethoxazole/trimethoprim (SMZ/TMP)

SMZ/TMP consist of two synergistic antibiotics that are active against a variety of bacteria including aerobic Gram-positive organisms.^{8,29,30} TMP and SMZ are both bacteriostatic when used alone but bactericidal when used in combination.^{31,32}

6 | TETRACYCLINE DERIVATIVES (DOXYCYCLINE, MINOCYCLINE, TIGECYCLINE)

6.1 | Doxycycline and minocycline

Doxycycline is a tetracycline derivative used to treat Gram-positive and -negative bacteria.^{8,33} Minocycline is also a tetracycline derivative with activity against aerobic Gram-positive and -negative bacteria.³⁴ Doxycycline and minocycline are both bacteriostatic.^{33,34} The PD measure of both doxycycline and minocycline is AUC/MIC.¹⁸

6.2 | Tigecycline

Tigecycline is a tetracycline derivative, glycylcycline antibiotic with activity against MSSA and MRSA.^{8,35} Tigecycline is bacteriostatic against *S. aureus*.³⁵ The PD measure of tigecycline is AUC/MIC.³⁵

7 | RESULTS OF CF ANTIBIOTIC UTILIZATION SURVEYS

A recent survey by Zobell et al.² documented the utilization of antibiotics for MRSA among Cystic Fibrosis Foundation-accredited care centers in the treatment of APE. The most commonly utilized MRSA antibiotic in the outpatient setting was oral SMZ/TMP in both pediatric (109/287, 38%) and adult (99/295, 34%) patients.² It was noted that 10% of SMZ/TMP was used in combination with rifampin (Table 1).² In the inpatient setting, the most commonly used antibiotic for both pediatric (oral 41/224, 18%; intravenous [IV] 35/224, 16%) and adult patients (oral 38/235, 16%; IV 44/235, 19%) was oral and IV linezolid (Table 2).

8 | CF ANTIBIOTIC DOSING RECOMMENDATIONS: MRSA

Dosing recommendations for MRSA have been published by the European Consensus Committee, the United Kingdom (UK) CF Trust Working Group, and Infectious Disease Society of America (IDSA) (Table 3).^{21,38,42} These recommendations vary but may be higher than Food and Drugs Administration (FDA)-approved doses. The differences in doses may reflect the PK/PD differences amongst CF and non-CF patients.

9 | EVIDENCE-BASED DOSING RECOMMENDATIONS: MRSA

9.1 | Ceftaroline

The literature does not support the FDA-approved dosing recommendations (Table 4). The PK/PD studies performed in pediatric and adult patients showed these dosing regimens are insufficient to treat MRSA in CF patients and higher or more frequent dosing may be needed (Table 4).^{9,36,43-45} Further studies are needed to determine the efficacy and tolerability of these dosing regimens in pediatric and adult CF patients (Table 4).

9.2 | Clindamycin

The literature does not support the European, UK CF Trust, IDSA, or FDA-approved dosing recommendations for clindamycin.^{21,37,38,42,56} A clindamycin PK case report of an adult patient with CF reported slower oral absorption rates when compared to healthy patients.⁴⁶ No data exists describing the PD, efficacy, or tolerability of clindamycin in patients with CF. Furthermore, a high rate of constitutive and inducible resistance limits the clinical utility of clindamycin in MRSA infections in patients with CF.¹¹⁻¹³ On the basis of limited PK/PD, efficacy, or tolerability data, recommendations about the use of clindamycin in the treatment of APE are based on FDA-approved or guideline recommendations (Table 4).^{21,37,38,42,56} In addition, clindamycin is recommended to be used in combination with additional susceptible antibiotic(s) to prevent the development of resistance (Table 4). Future studies are needed to determine the PK/PD, efficacy, and tolerability for the treatment of APE in pediatric and adult CF patients.

TABLE 1 Oral outpatient utilization rates and reported respondent dosing regimens for anti-MRSA antibiotics in CF patients with chronic MRSA during an acute pulmonary exacerbation² ($n = 94$)^a

Antibiotic	Pediatric utilization n (%)	Adult utilization n (%)	Reported pediatric dose ^b (mg/kg/day)	Reported adult dose ^b (mg)	Reported max dose ^b (mg/day)
SMZ/TMP	89 (31)	89 (30.2)	5–40 div every 8–12 h	160–320 every 8–24 h	960
Linezolid	77 (27)	83 (28.1)	5–30 div every 8–12 h	600 every 8–12 h	1800
Doxycycline	31 (11)	48 (16.3)	2–5 div every 12–24 h	100–200 every 12–24 h	400
Clindamycin	29 (10)	13 (4.4)	10–40 div every 6–8 h	300–600 every 6–8 h	2400
Minocycline	15 (5)	18 (6.1)	4 div every 12 h	100–200 every 12–24 h	400
SMZ/TMP + rifampin	20 (7)	10 (3.4)	SMZ/TMP 8–40 div every 8–12 h; rifampin 10–20 div every 12 h	SMZ/TMP 160–320 every 8–12 h; rifampin 300–600 every 12–24 h	SMZ/TMP 960; rifampin 1200
Ciprofloxacin	12 (4.1)	17 (5.7)	30–50 div every 12 h	500–1000 every 12 h	2250
Levofloxacin	10 (3.5)	15 (5.1)	10–30 div every 12–24 h	500–750 every 12–24 h	1500
Doxycycline + rifampin	4 (1.4)	2 (0.7)	Doxycycline 2–4 div every 12 h; rifampin 15 div every 12 h	Doxycycline 100 every 12 h; rifampin 300 every 12 h	Doxycycline 200; rifampin 600

Abbreviations: CF, cystic fibrosis; div, divided; MRSA, methicillin-resistant *Staphylococcus aureus*; SMZ/TMP, sulfamethoxazole/trimethoprim.

^aRespondents were able to choose the three most commonly utilized antibiotics.

^bThe doses are what was reported by respondents and may not be consistent with recommended dosing guidelines.

TABLE 2 Inpatient utilization rates and reported respondent dosing regimens for anti-MRSA antibiotics in CF patients with chronic MRSA during an acute pulmonary exacerbation² (n = 74 pediatric and 76 adult respondents)^a

Antibiotic	Pediatric utilization (%)	Adult utilization (%)	Reported pediatric dose ^b (mg/kg/day)	Reported adult dose ^b (mg)	Reported max dose ^b (mg/day)
Linezolid IV	35 (16)	44 (19)	5–30 div every 8–12 h	300–600 every 8–12 h	1800
Linezolid oral	41 (18)	38 (16)	10–30 div every 8–12 h	300–600 every 8–12 h	1800
Vancomycin IV	70 (31)	71 (30)	20–200 div every 6–12 h	500–2000 every 6–12 h	6000
SMZ/TMP oral	28 (13)	33 (14)	6–20 div every 8–12 h	160–320 every 8–12 h	960
Rifampin oral	28 (13)	1 (0.4)	10–20 div every 12–24 h	600 every 12 h	1200
SMZ/TMP IV	9 (4)	9 (3.7)	10–20 div every 8–12 h	160–320 every 8–12 h	960
Clindamycin IV	9 (4)	4 (1.7)	20–40 div every 8–12 h	375–900 every 6–8 h	3600
Doxycycline oral	4 (1.8)	9 (3.7)	4.4 div every 12 h	100 every 12 h	200
Levofloxacin IV	7 (3)	5 (2)	10–20 div every 12–24 h	500–750 every 12–24 h	1500
Ceftaroline IV	3 (1.3)	4 (1.7)	5–20 div every 12 h	600–1000 every 8–12 h	3000
Minocycline oral	4 (1.8)	3 (1.3)	4 div every 12 h	100–200 every 12 h	400
Tigecycline IV	2 (0.9)	5 (2)	1.7 div every 12 h	100 every 12 h	200
Clindamycin oral	5 (2.2)	1 (0.4)	20–40 div every 6 h	150–600 every 8 h	1800
Rifampin IV	4 (1.8)	2 (0.8)	10–30 div every 12–24 h	600 every 24 h	1200
Doxycycline IV	3 (1.3)	1 (0.4)	5 div every 12 h	100 every 12 h	200
Levofloxacin oral	2 (0.9)	2 (0.8)	20 div every 12 h	750 every 24 h	750
Ciprofloxacin oral	2 (0.9)	1 (0.4)	20–40 div every 8–12 h	500–750 every 8–12 h	1800
Ciprofloxacin IV	NA	1 (0.4)	NA	400 every 8–12 h	1200
Telavancin IV	NA	1 (0.4)	NA	20 mg/kg/day div every 12 h	20 mg/kg/day div every 12 h

Abbreviations: CF, cystic fibrosis; div, divided; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; Sulfa/TMP, sulfamethoxazole/trimethoprim.

^aRespondents were able to choose the three most commonly utilized antibiotics.

^bThe doses are what was reported by respondents and may not be consistent with recommended dosing guidelines.

10 | FLUOROQUINOLONE DERIVATIVES (CIPROFLOXACIN, LEVOFLOXACIN)

The literature does not support the dosing recommendations for ciprofloxacin and levofloxacin for the treatment of MRSA infections and are not routinely recommended due to the emergence of resistance.^{2,8,21} Future studies are needed to determine the PK/PD, efficacy, and tolerability of these antibiotics in pediatric and adult CF patients.

11 | GLYCOPEPTIDE DERIVATIVES (TELAVANCIN, VANCOMYCIN)

11.1 | Telavancin

There is limited data on the use of telavancin for MRSA infections in CF patients. Results from the antibiotic utilization survey, report

higher (adult: 20 mg/kg/day every 12 h, max 20 mg/kg/day every 12 h) than the FDA-dosing recommendations (Tables 3 and 4).^{2,19} Further PK/PD, efficacy, and tolerability studies are needed in adult CF patients. There is currently no data in pediatric patients.

11.2 | Vancomycin

The literature does not support the UK CF Trust dosing recommendations for IV vancomycin or the FDA-approved dosing recommendations.^{20,42} The limited PK/PD studies performed in pediatric and adult patients showed that these dosing regimens were not sufficient and that higher or more frequent dosing (pediatric: 70–80 mg/kg/day divided every 6 h, maximum 4000 mg/day; adult: 30–45 mg/kg/day, divided every 8–12 h, maximum 4000 mg/day) may be needed to achieve AUC/MIC levels above 400 (Table 4).^{47–51} Further studies are needed to determine the efficacy and tolerability of these dosing regimens in pediatric and adult CF patients.

TABLE 3 Summary of antibiotic FDA-approved, consensus, and guideline dose recommendations

Antibiotic	Source	Pediatric dose	Maximum pediatric dose (mg/day)	Adult dose	Maximum adult dose (mg/day)
Ceftaroline IV	FDA-approved ⁹	Age 2 months to <2 years; 8 mg/kg every 8 h Age ≥ 2 to <18 years weighing ≤ 33 kg; 12 mg/kg every 8 h Age ≥ 2 to <18 years weighing > 33 kg; 400 mg every 8 or 6 h	1200	600 mg IV every 12 h	1200
Clindamycin IV	FDA-approved ³⁷	20–40 mg/kg/day div every 6–8 h	2700	1200–2700 mg/day div every 6–8 h	2700
	European Consensus ³⁸	20–40 mg/kg/day div every 6–12 h	1800	20–40 mg/kg/day div every 6–12 h	1800
	IDSA ²¹	40 mg/kg/day div every 6–8 h	1800	600 mg every 8 h	1800
Clindamycin oral	FDA-approved ⁵⁶	8–20 mg/kg/day div every 6–8 h	1800	150–450 mg every 6 h	1800
	European Consensus ³⁸	20–40 mg/kg/day div every 6–12 h	1800	20–40 mg/kg/day div every 6–12 h	1800
	UK CF Trust Guideline ³⁸	20–28 mg/kg/day div every 6 h, max 600 mg every 6 hrs	2400		2400
Ciprofloxacin IV ^a	FDA-approved ¹⁶	10–20 mg/kg every 12 h	750	400 mg every 8 h	1200 mg
Ciprofloxacin oral ^a	FDA-approved ¹⁶	10–20 mg/kg every 12 h	750	500–750 mg every 12 h	1500 mg
Levofloxacin IV ^b	FDA-approved ¹⁷	30–49 kg: 250 mg every 12 h 50 kg or >500 mg	500	750 mg every 24 h	750 mg
Levofloxacin oral ^a	FDA-approved ¹⁷	30–49 kg: 250 mg every 12 h 50 kg or >500 mg	500	750 mg every 24 h	750 mg
Telavancin IV	FDA-approved ¹⁹	No data	No data	10 mg/kg every 24 h	10 mg/kg
Vancomycin IV	FDA-approved ²⁰	10 mg/kg/dose every 6 h		500–1000 mg every 12 h	2000
	UK CF Trust Guideline ⁴²	15 mg/kg/dose every 8 h	2000	1000 mg every 12 h	2000
Linezolid IV	FDA-approved ²²	30 mg/kg/day div every 8–12 h	1200	600 mg every 12 h	1200
	UK CF Trust Guideline ⁴²	30 mg/kg/day div every 8 h	1800	600 mg every 12 h	1200
Rifampin IV	FDA-approved ²⁵	10–20 mg/kg/day div every 12–24 h	600	600 mg every 24 h	600
	European Consensus ³⁸	15–20 mg/kg/day div every 12–24 h	600	15–20 mg/kg/day div every 12 h	600
Rifampin oral	FDA-approved ²⁶	10–20 mg/kg/day div every 12–24 h	600	10 mg/kg/day every 24 h	600
	European Consensus ³⁸	15–20 mg/kg/day div every 12–24 h	600	15–20 mg/kg/day div every 12–24 h	600

(Continues)

TABLE 3 (Continued)

Antibiotic	Source	Pediatric dose	Maximum pediatric dose (mg/day)	Adult dose	Maximum adult dose (mg/day)
Sulfamethoxazole-Trimethoprim IV	FDA-approved ³⁰	15–20 mg/kg/day div every 6–8 h (based on TMP)	960	15–20 mg/kg/day div every 6–8 h	960
Sulfamethoxazole-Trimethoprim oral	FDA-approved ²⁹ European Consensus ³⁸	15–20 mg/kg/day div every 6 h (based on TMP) 8–10 mg/kg/day div every 12 h (based on TMP)	960 320	15–20 mg/kg/day div every 6 h 8–10 mg/kg/day div every 12 h	960 320
Doxycycline IV	FDA-approved ³³	Severe or life-threatening infections: Anthrax, Rocky Mountain spotted fever Children weighing < 45 kg: 2.2 mg/kg every 12 h Children weighing ≥ 45 kg: should receive the adult dose Less severe disease: Age ≥ 8 years and weighing < 45 kg: 4.4 mg/kg/day div every 12 h on Day 1, followed by 2.2 mg/kg given as single daily dose or div every 12 h	200	200 mg on Day 1, followed by 100 to 200 mg daily dose depending on the severity of infection	200
Doxycycline oral	FDA-approved ⁴⁰	Severe or life-threatening infections: Anthrax, Rocky Mountain spotted fever Children weighing < 45 kg: 2.2 mg/kg every 12 h Children weighing ≥ 45 kg: should receive the adult dose Less severe disease: Age ≥ 8 years and weighing < 45 kg: 4.4 mg/kg/day div every 12 h on Day 1, followed by 2.2 mg/kg given as single daily dose or div every 12 h	Age ≥ 8 years: 1 to 2 mg/kg/dose twice daily	100 mg every 12 h	200
Minocycline IV	FDA-approved ⁴¹	Age > 8 years; 4 mg/kg once, then 2 mg/kg/dose every 12 h	400	200 mg × 1 dose, then 100 mg IV every 12 h	400
Minocycline oral	FDA-approved ⁹³	Age > 8 years; 4 mg/kg once, then 2 mg/kg/dose every 12 h	200	200 mg × 1 dose, then 100 mg every 12 h	200
Tigecycline IV	FDA-approved ³⁵	Age 8–11 years; 1.2 mg/kg every 12 h Age 12–17 years: 50 mg every 12 h	100	100 mg once, then 50 mg every 12 h	100

Abbreviations: div, divided; FDA, Food and Drugs Administration; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral.

^aFluoroquinolones are not recommended for the treatment of MRSA due to the development of rapid resistance.

TABLE 4 Evidence-based dosing summary of anti-MRSA antibiotics in pediatric and adult CF patients

Antibiotic	Pediatric dose (mg/kg/day)	Adult dose (mg/dose)	Reported maximum dose (mg/day)
Ceftaroline ^{42–45}	10–15 div every 8 h infused over 1–3 h	15 mg/kg/dose (max 600 mg) every 8 h over 1–3 h	1800
Clindamycin IV ^{21,37,38,42}	20–40 div every 6–8 h	600–900 every 6–8 h	1800–2700
Clindamycin oral ^{37,56,a}	20–40 div every 6–8 h	600 every 6–8 h	2400
Fluoroquinolones			
Ciprofloxacin ²¹	Not recommended		
Levofloxacin ²¹	Not recommended		
Glycopeptides			
Telavancin ²	NR	20 mg/kg/day every 12 h	20 mg/kg/day every 12 h
Vancomycin ^{47–51}	60–80 div every 6 h	30–45 mg/kg/day div every 8–12 h	4000
Linezolid ^{22,38,52,57}	30–45 div every 8 h	600 every 8 h	1800
Rifampin IV ^{25,38,54,a}	10–30 div every 12–24 h	600 every 24 h	600
Rifampin oral ^{26,38,54,a}	10–20 div every 12–24 h	600 every 24 h	600
Sulfamethoxazole/Trimethoprim IV ^{30,38,42,b}	15–20 div every 6–8 h (based on TMP)	160–320 every 8 h	960
Sulfamethoxazole/Trimethoprim oral ^{29,38,42,b}	15–20 div every 6–8 h (based on TMP)	160–320 every 8 h	960
Tetracyclines			
Doxycycline IV ^{2,33,38,68}	5 div every 12 h	100 every 12 h	200
Doxycycline oral ^{2,38,40,68}	4.4 div every 12 h	100 every 12 h	200
Minocycline IV ²	Age > 8 years; 4 mg/kg × 1 dose, then 4 div every 12 h	200 × 1 dose, then 100 every 12 h	400
Minocycline oral ^{2,93}	4 div every 12 h	100–200 mg every 12 h	400
Tigecycline ²	1.7 every 12 h	100 mg every 12 h	200

Note: Fluoroquinolones are not recommended for the treatment of MRSA due to the development of rapid resistance.

Abbreviations: IV, intravenous; div, divided; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, Not recommended; TMP, trimethoprim.

^aRecommended to be used in combination with additional susceptible antibiotic(s) to prevent the development of resistance (53, 79).

^bOn the basis of trimethoprim component.

11.3 | Linezolid

The literature does not support the UK CF Trust dosing recommendations for oral/IV linezolid or the FDA-approved dosing recommendations for the treatment of MRSA infections (Table 3).^{22,42} The PK/PD studies performed in pediatric and adult patients showed that these dosing regimens were not sufficient and that higher or more frequent dosing (pediatric: 15 mg/kg/dose every 8 h, max 1800 mg/day; adult: 600 mg every 8 h, max 1800 mg/day) may be needed to adequately reach the appropriate PD target of AUC/MIC > 80.^{23,52,57} Further studies are needed to determine the efficacy and tolerability of these dosing regimens in pediatric and adult CF patients. The risk of the development of linezolid-resistant *S. aureus* is a concern that may limit the usefulness of linezolid in the treatment of MRSA in CF patients (Table 4).^{53,58–65}

11.4 | Rifampin

The literature does not support the European, UK CF Trust, IDSA, or FDA-approved dosing recommendations for rifampin.^{25,26,38,54} There is currently one published study regarding the use of rifampin as adjunctive therapy for the treatment of APE in CF patients colonized with MRSA.⁵⁴ Rifampin in combination with vancomycin did not provide clinical benefit when compared to vancomycin monotherapy for the treatment of APE in patients with CF.⁵⁴ Unfortunately, the authors did not report any rifampin PK/PD data. The optimal dose of rifampin in CF patients infected with MRSA is unclear due to the lack of PK/PD, efficacy, and tolerability studies. In addition, high rates of resistance and unwanted adverse effects may limit the clinical utility of rifampin. Furthermore, rifampin induces numerous cytochrome P450 (CYP) enzymes, which may result in reduced serum concentrations of drugs that are metabolized through the CYP enzyme

TABLE 5 Evidence-based dosing summary of ABPA medications for pediatric and adult CF patients

Medication	Dose mg/kg/day	Max dose mg/day
Corticosteroids ⁹⁴	0.5-2 oral prednisone equivalent	60
Nebulized amphotericin B	Insufficient evidence for recommendation	Insufficient evidence for recommendation
Isavuconazole	Insufficient evidence for recommendation	Insufficient evidence for recommendation
Itraconazole	Insufficient evidence for recommendation	Insufficient evidence for recommendation
Posaconazole	Insufficient evidence for recommendation	Insufficient evidence for recommendation
Voriconazole	Insufficient evidence for recommendation	Insufficient evidence for recommendation
Omaliuzumab	Insufficient evidence for recommendation	Insufficient evidence for recommendation

system. On the basis of limited PK/PD, efficacy, or tolerability data, recommendations about the use of rifampin in the treatment of APE are based on FDA-approved or guideline recommendations (Table 4).^{25,26,38,54} Rifampin should only be used as adjunctive therapy and not monotherapy. Future studies are needed to determine the PK/PD, efficacy, and tolerability in pediatric and adult CF patients.

12 | SULFAMETHOXAZOLE/TRIMETHOPRIM (SMZ/TMP)

Limited SMZ/TMP PK studies in adolescent and adult patients with CF reported that higher total daily doses or more frequent dosing intervals (e.g., every 8 vs. 12 h) may be required due to higher clearance rates than healthy controls.⁶⁶ The optimal dose of SMZ/TMP in CF patients colonized with MRSA is uncertain due to the lack of PK/PD, efficacy, and tolerability studies. Furthermore, increasing rates of resistance and its ability to increase the risk for developing small colony-variant infections may limit its clinical use.^{12,55,67} On the basis of limited PK/PD, efficacy, or tolerability data, recommendations about the use of SMZ/TMP in the treatment of APE are based on FDA-approved or guideline recommendations (Table 4).^{29,30,38,42,66} Future studies are needed to determine the PK/PD, efficacy, and tolerability in pediatric and adult CF patients.

13 | TETRACYCLINE DERIVATIVES (DOXYCYCLINE, MINOCYCLINE, TIGECYCLINE)

In a PK/PD analysis by Beringer et al.,⁶⁸ doxycycline produced a PK profile similar to non-CF patients. Concentrations of doxycycline given at the highest dose of 200 mg/day produced anti-inflammatory effects and should be evaluated in clinical trials.⁶⁸ There are currently no efficacy studies regarding the use of doxycycline in the treatment of APE in patients with CF. On the basis of limited PK/PD, efficacy, or tolerability data, recommendations about the use of doxycycline in the treatment of APE are based on FDA-approved or guideline recommendations (Table 4).^{2,33,38,68} Future studies are needed to determine the PK/PD, efficacy, and tolerability in pediatric and adult CF patients.

In a retrospective study involving a 2-year antibiotic cycle, CF patients took minocycline for 3 months and experienced weight

gain.³⁴ Minocycline was not used for the treatment of exacerbations in this study. Patients received 50 mg daily ($n = 1$), 50 mg twice daily ($n = 1$), 100 mg daily ($n = 13$), 100 mg twice daily ($n = 84$), or 100 mg three times daily ($n = 1$).³⁴ Some patients received more than one cycle of minocycline in their rotation.³⁴ More than half of the patients taking 100 mg twice daily reported decreased cough and sputum production.³⁴ The same dosing regimens were reported for pediatric and adult patients in both the outpatient and inpatient settings (Tables 1 and 2).² Future studies are needed to determine the PK/PD, efficacy, and tolerability in pediatric and adult CF patients.

There is limited data on the use of tigecycline for MRSA infections in CF patients. Results from the antibiotic utilization survey report higher doses (pediatric: 1.7 mg/kg/day divided every 12 h, max of 200 mg/day; adult 100 mg every 12 h) of tigecycline in CF patients in comparison to the FDA-approved dosing recommendations (Tables 3 and 4).^{2,35} Further PK/PD, efficacy, and tolerability studies are needed in pediatric and adult CF patients.

14 | ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

A. fumigatus is another organism found in the airways of CF patients. ABPA is a hypersensitivity reaction caused by the colonization of *A. fumigatus* in the lungs.³ ABPA is a common complication in patients with CF and can lead to accelerated decline in lung function if untreated.³ It is estimated that the prevalence of patients with CF who develop ABPA is between 1% and 15%.^{4,5} On chest radiography, ABPA typically presents as asthma with infiltrates and proximal bronchiectasis.⁴ Poor nutritional status is a risk factor for ABPA in CF patients, whereas long-term azithromycin use is associated with *Aspergillus* colonization.⁴

15 | DESCRIPTION OF MEDICATIONS USED FOR ABPA

15.1 | Corticosteroids

Corticosteroids have a wide variety of indications and are used primarily for their anti-inflammatory effect.^{69,70}

15.2 | Nebulized amphotericin B

Amphotericin B is an antifungal antibiotic obtained from *Streptomyces nodosus*.⁶⁹

Amphotericin B is only commercially available as an IV solution in various forms and not as a nebulized product. The IV solutions have been used “off-label” for inhalation by nebulization. These various IV formulations are conventional amphotericin B, amphotericin B lipid complex (Abelcet®), liposomal amphotericin B (Ambisome®).^{71–73} All of these formulations are indicated for the treatment of progressive, life-threatening fungal infections caused by *Histoplasma capsulatum*, *Coccidioides immitis*, *Candida* sp., *Blastomyces dermatitidis*, *Rhodotorula*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Mucor mucedo*, and *A. fumigatus*.^{71–73}

15.3 | Isavuconazole

Isavuconazole is a member of the azole class of antifungals indicated for the treatment of invasive aspergillosis and invasive mucormycosis.^{69,74} Isavuconazonium sulfate is a prodrug of isavuconazole.

15.4 | Itraconazole

Itraconazole is a member of the azole class of antifungals with both oral suspension and capsules indicated for the treatment of pulmonary and extrapulmonary fungal infections in both immunocompromised and nonimmunocompromised patients caused by *B. dermatitidis*, *Histoplasma* sp., and *Aspergillus* sp.^{69,75} Itraconazole solution and capsules are not interchangeable due to differences in bioavailability as a result of the effects of gastric acidity as well as absorption kinetics. Hydroxyitraconazole is the bioactive metabolite of itraconazole.⁷⁵ Therapeutic drug monitoring utilizing serum itraconazole trough concentrations is routinely recommended with a range of over 0.5 to 1 µg/ml.⁷⁵ The method of concentration measurement may alter the results received due to the presence of the hydroxyitraconazole. If plasma concentrations are measured by high-performance liquid chromatography, the reported concentrations values are specifically itraconazole.⁷⁵ If bioassay is used, the values are 3.3 times higher due to the presence of hydroxyitraconazole.⁷⁵

15.5 | Posaconazole

Posaconazole is a member of the azole class of antifungals. Posaconazole injection, delayed-release tablets, and oral suspension are indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients at high risk of developing such infections.^{69,76} Posaconazole oral suspension is FDA-approved for the treatment of oropharyngeal candidiasis including oropharyngeal candidiasis resistant to itraconazole and/or

fluconazole.⁷⁶ Differences in bioavailability exist between posaconazole delayed-release tablets and oral suspension. Thus, the delayed-release tablets and oral suspension are not interchangeable and the manufacturer-specific dosage recommendations for each formulation should be followed.⁷⁶ Posaconazole delayed-release tablets should be taken with food to enhance absorption and optimize plasma concentrations.⁷⁶ Posaconazole oral suspension should be taken during or immediately (within 20 min) following a meal to enhance absorption and optimize plasma concentrations.

15.6 | Voriconazole

Voriconazole is a member of the azole class of antifungals. Voriconazole IV solution, oral suspension, and tablets are indicated for the treatment of invasive aspergillosis (from *A. fumigatus*), *Candidemia* in nonneutropenic patients, and other deep tissue *Candida* infections, esophageal candidiasis, and *Scedosporiosis* and *Fusariosis*.^{69,77} The PK profiles of voriconazole are similar when administered via IV and oral routes.⁷⁷ Maximum plasma concentrations (C_{max}) of oral voriconazole are decreased if taken with a high-fat meal (i.e., 34% suspension, 58% tablet). Thus, for optimal absorption, oral voriconazole doses are recommended to be taken 1 h before or after meals.⁷⁷

15.7 | Omalizumab

Omalizumab is a monoclonal antibody that selectively binds to human immunoglobulin E (IgE).^{69,78} It is FDA-approved for asthma and chronic idiopathic urticaria.⁷⁸ Omalizumab is available as a 75-mg/0.5-ml (0.5 ml), 150-mg/ml (1-ml)-prefilled syringes and 150-mg lyophilized powder for reconstitution all for subcutaneous administration.

16 | CF DOSING RECOMMENDATIONS: ABPA

A number of case reports have been published describing the use of various medications for ABPA. However, there is insufficient evidence to make medication dosage recommendations as there is a lack of PK/PD studies and randomized controlled studies for pediatric and adult CF patients.

17 | EVIDENCE-BASED SUMMARY: ABPA

17.1 | Corticosteroids

Neither PK/PD studies nor randomized controlled studies have been performed in pediatric and adult CF patients, only several case reports. Further studies are needed to determine the PK/PD, efficacy, and tolerability.

17.2 | Nebulized amphotericin B

Neither PK/PD studies nor randomized controlled studies have been performed in pediatric and adult CF patients, only several case reports. Further studies are needed to determine the PK/PD, efficacy, and tolerability.

17.3 | Isavuconazole

Neither PK/PD studies nor randomized controlled studies have been performed in pediatric and adult CF patients, only several case reports. Further studies are needed to determine the PK/PD, efficacy, and tolerability.

17.4 | Itraconazole

The PK/PD studies performed in pediatric and adult patients showed these dosing regimens may not be sufficient to obtain therapeutic itraconazole serum concentrations in CF patients and higher or more frequent dosing may be needed.^{79–82} Efficacy of itraconazole was not shown in a double-blind, randomized, placebo-controlled trial conducted by Aaron et al.⁸² Further studies are needed to determine the efficacy and tolerability in pediatric and adult CF patients.

17.5 | Posaconazole

The literature does support the FDA-approved dosing recommendations based upon one single-center, nonrandomized study.⁸³ Further studies are needed that evaluate PK/PD, efficacy, and tolerability.

17.6 | Voriconazole

The PK/PD studies performed in pediatric and adult patients demonstrated that higher or more frequent dosing may be needed in CF patients to obtain therapeutic voriconazole serum concentrations.^{84–89} In addition, there is wide inpatient variability in voriconazole metabolism that may also be influenced by CYP2C19 polymorphisms.^{87,88} As a result, therapeutic drug monitoring is recommended. There is a paucity of data regarding the efficacy of voriconazole for the treatment of ABPA in patients with CF. Efficacy of voriconazole has been limited to case reports and small retrospective case series, thus, further studies are needed to determine the efficacy and tolerability in pediatric and adult CF patients.

17.7 | Omalizumab

Neither PK/PD studies nor randomized controlled studies have been performed in pediatric and adult CF patients, only several case

reports. Further studies are needed to determine the PK/PD, efficacy, and tolerability.

18 | PK AND PD OF ANTIMICROBIALS IN CF PATIENTS

Patients with CF may require higher doses of antimicrobials compared to patients without CF. This is due to CF patients having a larger volume of distribution and rapid renal clearance.^{90,91} This results in the need for higher and more frequent dosing to achieve appropriate serum concentrations of antibiotics.^{90,91} The efficacy and tolerability of these antimicrobial agents are variable. A review of these studies can be found in parts I–II of this series.^{8,69}

18.1 | Rationale for PK/PD studies

Antibiotics are essential in the care of CF patients. It is prudent to utilize antibiotic regimens that will be most efficacious while minimizing adverse effects. Utilizing PK/PD data is a way to enhance dose optimization of antimicrobials. PK/PD index (e.g., AUC/MIC, T > MIC) describes the relationship between PK parameters and microbiological parameters.⁹² The MIC is a standard reference used to predict bacterial eradication or treatment success.³⁹ Knowledge of the relationship between antibiotic concentration to microbiological potency and the effect on antibacterial activity can lead to a dosing regimen that optimizes the killing of bacteria.¹⁸

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Quovadis J Epps: Project administration (equal); supervision (equal); writing original draft (equal); writing review & editing (equal). **Kevin L. Epps:** Writing original draft (equal); writing review & editing (equal). **David C. Young:** Conceptualization (equal); project administration (equal); writing original draft (equal); writing review & editing (equal). **Jeffery T. Zobell:** conceptualization (equal); project administration (equal); writing original draft (equal); writing review & editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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