Optimal Therapeutic Drug Monitoring Strategy for IV Aminoglycosides and IV Vancomycin in People with Cystic Fibrosis: A Systematic Review

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ABSTRACT

Background: Given altered pharmacokinetics in people with cystic fibrosis (pwCF), there is debate regarding optimal strategies for therapeutic drug monitoring (TDM) for aminoglycosides and vancomycin administered intravenously.

Objectives: To determine the TDM strategy for IV aminoglycosides and IV vancomycin associated with optimal clinical outcomes in pwCF.

Data Sources: Several databases (MEDLINE, Embase, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov) were searched from inception to November 15, 2020, with searches rerun on February 13, 2023.

Study Selection and Data Extraction: Full articles evaluating TDM strategies and clinical outcomes in pwCF receiving IV aminoglycosides or IV vancomycin were included.

Data Synthesis: Three studies met the inclusion criteria for IV aminoglycosides, and 1 study met the inclusion criteria for IV vancomycin. Data are presented with descriptive analyses.

Conclusions: The available evidence is insufficient to determine an optimal TDM strategy for IV aminoglycoside or IV vancomycin therapy in pwCF.

Keywords: cystic fibrosis, therapeutic drug monitoring, aminoglycosides, vancomycin, systematic review

RÉSUMÉ

Contexte : Étant donné que la pharmacocinétique des personnes atteintes de fibrose kystique est altérée, un débat existe concernant les stratégies optimales de suivi thérapeutique des médicaments (STM) pour les aminoglycosides et la vancomycine administrés par voie intraveineuse.

Objectif : Déterminer la stratégie de suivi thérapeutique des médicaments pour les aminoglycosides et la vancomycine par voie intraveineuse associée aux résultats cliniques optimaux chez les personnes atteintes de fibrose kystique.

Sources des données : Plusieurs bases de données (MEDLINE, Embase, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials et ClinicalTrials.gov) ont été consultées depuis leur création jusqu'au 15 novembre 2020, avec des recherches répétées le 13 février 2023.

Sélection des études et extraction des données : Les articles en texte intégral évaluant les stratégies de suivi thérapeutique des médicaments et les résultats cliniques chez les personnes atteintes de fibrose kystique recevant des aminoglycosides ou de la vancomycine par voie intraveineuse ont été inclus.

Synthèse des données : Trois études répondaient aux critères d'inclusion pour les aminoglycosides par voie intraveineuse, et une étude répondait aux critères d'inclusion pour la vancomycine par voie intraveineuse. Les données s'accompagnent d'analyses descriptives.

Conclusions : Les éléments probants disponibles sont insuffisants pour déterminer une stratégie optimale de suivi thérapeutique des médicaments pour la thérapie par aminoglycosides par voie intraveineuse ou la vancomycine par voie intraveineuse chez les personnes atteintes de fibrose kystique.

Mots-clés : fibrose kystique, suivi thérapeutique des médicaments, aminoglycosides, vancomycine, revue systématique, suivi thérapeutique pharmacologique

INTRODUCTION

People with cystic fibrosis (pwCF) are prone to bacterial respiratory infections, which result in chronic inflammation and pulmonary exacerbations.[1] These problems lead to progressive decline in lung function and ultimately respiratory failure, which is the most common cause of death in pwCF.[2] As such, optimal antibiotic dosing is imperative. Antibiotic dosing in pwCF may be complicated by higher clearance and volume of distribution,[1,3] which in turn may necessitate higher doses relative to populations without cystic fibrosis (CF).[4] Dosing of certain antibiotics is optimized with therapeutic drug monitoring (TDM). Two of the most commonly used antibiotics in pwCF are aminoglycosides and vancomycin, administered intravenously.[5]

Aminoglycosides are concentration-dependent bactericidal agents.[6] In non-CF populations, a target ratio of maximum serum concentration (C_{max}) to minimum

inhibitory concentration (MIC) (C_{max}/MIC) of 8–10 has been associated with better clinical outcomes.[6,7] The ratio of area under the curve (AUC) to MIC (AUC/MIC) has also been associated with better outcomes.[8,9] Three reviews have summarized aminoglycoside pharmacokinetics and pharmacodynamics (PK/PD) and TDM for pwCF,[10-12] but the determination of optimal monitoring strategies was identified as a topic in need of further study.[10,12]

Vancomycin is a time-dependent bactericidal agent.[13] Recent updates to guidelines for serious methicillin-resistant *Staphylococcus aureus* infections have recommended AUC/MIC-based monitoring in place of previously recommended trough-based monitoring.[14] A systematic review challenged this recommendation because of inconsistent data showing benefit.[15] Two reviews have examined IV vancomycin PK and TDM in pwCF, but neither addressed clinical outcomes.[11,16]

To our knowledge, no review of this topic to date has applied a systematic methodology. The objective of this systematic review was to determine whether there is a TDM strategy for pwCF receiving IV aminoglycosides or IV vancomycin that optimizes clinical outcomes.

METHODS

Search Strategy

The MEDLINE, Embase, CINAHL, Web of Science Core Collection, and ClinicalTrials.gov databases were systematically searched up to November 15, 2020; the search was later rerun to include literature up to February 13, 2023. The reference lists of relevant studies were reviewed for additional studies not identified in the database searches. The systematic review protocol was registered with PROSPERO (CRD42020212941).

Selection of Studies

Studies comparing TDM strategies and clinical outcomes in pwCF who received an IV aminoglycoside or IV vancomycin were included. To be eligible for inclusion, the TDM strategies had to be described in enough detail to be reproducible. Nonhuman and in vitro studies, studies without full published reports, and those not available in English were excluded. Pairs of authors independently screened all studies identified in both the initial (J.J., N.G.) and subsequent (J.J., R.D.) searches. Discrepancies were resolved by consulting 2 additional authors (V.S., R.D.).

Outcomes

The primary outcomes of interest were change in lung function (e.g., percent or absolute change in forced expiratory volume in 1 second [FEV_1]), percent baseline lung function at end of treatment, symptom resolution, radiographic changes, and toxicity. The secondary outcomes of interest were death, duration of hospitalization, time to achieve therapeutic drug levels, treatment failure, daily antibiotic exposure, antibiotic dosing regimen, and timing of antibiotic level(s) measurement relative to the dose.

Data Extraction and Management

Relevant data, including first author, year of publication, study design, participant characteristics, and clinical outcomes, were extracted and tabulated.

Quality Assessment

All of the included studies were assessed independently for risk of bias by 2 reviewers (J.J., N.G.), who used the National Heart, Lung, and Blood Institute (US) quality assessment tool for observational cohort and cross-sectional studies.[17] An overall rating of "good", "fair", or "poor" was assigned to each report after discussion and consensus. Discrepancies were resolved by consulting the third and fourth authors (V.S., R.D.).

Data Analysis

Descriptive analyses were used to assess the extracted data.

RESULTS

Therapeutic Drug Monitoring Strategy

Aminoglycosides

Of the 4030 records identified in the initial search, 1 study[18] met the inclusion criteria (Figure 1); 2 additional studies were identified in the subsequent search.[19,20] The characteristics of included studies are summarized in Table 1.

Burkhardt and others[18] compared extended-interval and conventional dosing of tobramycin, retrospectively correlating the AUC achieved during a 24-hour interval (AUC_{24})/MIC and C_{max}/MIC with lung function at day 14 of treatment. Both AUC_{24}/MIC and C_{max}/MIC had a log–linear relationship with percent predicted FEV_1 ($ppFEV_1$) (extended-interval dosing: $r^2 = 0.62$ and 0.31, respectively; conventional dosing: $r^2 = 0.63$ and 0.17, respectively).[18] For equal values of AUC_{24}/MIC, extended-interval dosing was associated with a higher $ppFEV_1$ at day 14 relative to conventional dosing.[18] The relationship between lung function improvement and C_{max}/MIC was not dependent on dosing interval.[18]

Landmesser and others[19] conducted a retrospective chart review comparing the predictive value of AUC_{24} and C_{max} for change in absolute FEV_1. Of patients who achieved an AUC_{24} of at least 80 mg*h/L, 75.8% had a return to baseline FEV_1, compared with 61.5% of those with an AUC_{24} less than 80 mg*h/L ($p = 0.147$).[19] Similarly, 80.3% of patients who achieved the target C_{max} of at least 8 times the highest-documented MIC for *Pseudomonas aeruginosa* had a return to baseline FEV_1, compared with 65.6% who did not achieve the aforementioned target C_{max}/MIC ($p = 0.065$).[19] Acute kidney injury (AKI) was more frequent among those who received multiple daily doses than among those with

extended-interval dosing ($p = 0.047$), but was not associated with increasing AUC_{24} or C_{max}.[19]

The ambidirectional cohort study by Hemmann and others[20] compared trough-only and patient-specific PK monitoring for tobramycin and amikacin using 2- and 8-hour post-dose levels. There was no significant difference between groups for change in $ppFEV_1$, antibiotic duration, length of stay, or nephrotoxicity.[20] In the patient-specific PK group, 75% of participants required dose adjustments after initial measurement of serum concentration, whereas none of those in the trough-only group required dose adjustments ($p < 0.001$); the majority of adjustments involved a decrease in dose interval to avoid a prolonged drug-free interval.[20]

Vancomycin

No studies identified in the initial search met the inclusion criteria (Figure 1), but 1 study was identified when the search was rerun. Mitchell and others[21] retrospectively compared trough- and AUC-based monitoring. Among adults, 86.5% in the AUC-based monitoring group and 56.5% in the trough-based monitoring group had a return to baseline $ppFEV_1$ ($p = 0.002$); notably, 50% of those with return to baseline in the AUC-based monitoring group and 20% in the trough-based monitoring group were receiving a CF transmembrane conductance regulator (CFTR) modulator.[21] Among pediatric patients, 67% in the AUC-based monitoring group and 80% in the trough-based monitoring group had return to baseline $ppFEV_1$ ($p = 0.458$), and among these patients, 58% in the AUC-based monitoring group and 75% in the trough-based monitoring groups were receiving a CFTR modulator.[21] Time to next exacerbation and AKI incidence were not significantly different between groups.[21] AKIs of higher severity occurred only in adults in the trough-based monitoring group; however, concomitant nephrotoxic medications were more prevalent in this group.[21] Median total daily dose for AUC- versus trough-based monitoring was 40 mg/kg and 52 mg/kg, respectively, among adults and 60 mg/kg and 58 mg/kg, respectively, among pediatric patients.[21] Overall, lower troughs were observed in the AUC group.[21]

Quality Assessment

Three of the included studies were deemed to be of "good" quality,[19-21] and 1 study was deemed to be of "fair" quality.[18]

DISCUSSION

The objective of this systematic review was to determine if there is a TDM strategy for IV aminoglycosides and IV vancomycin associated with optimal clinical outcomes in pwCF.

Aminoglycosides

Results from the 2 studies comparing C_{max} with AUC_{24} were conflicting.[18,19] Burkhardt and others[18] suggested that C_{max}/MIC may be a better measure for clinical outcomes, given that the relationship with $ppFEV_1$ was not affected

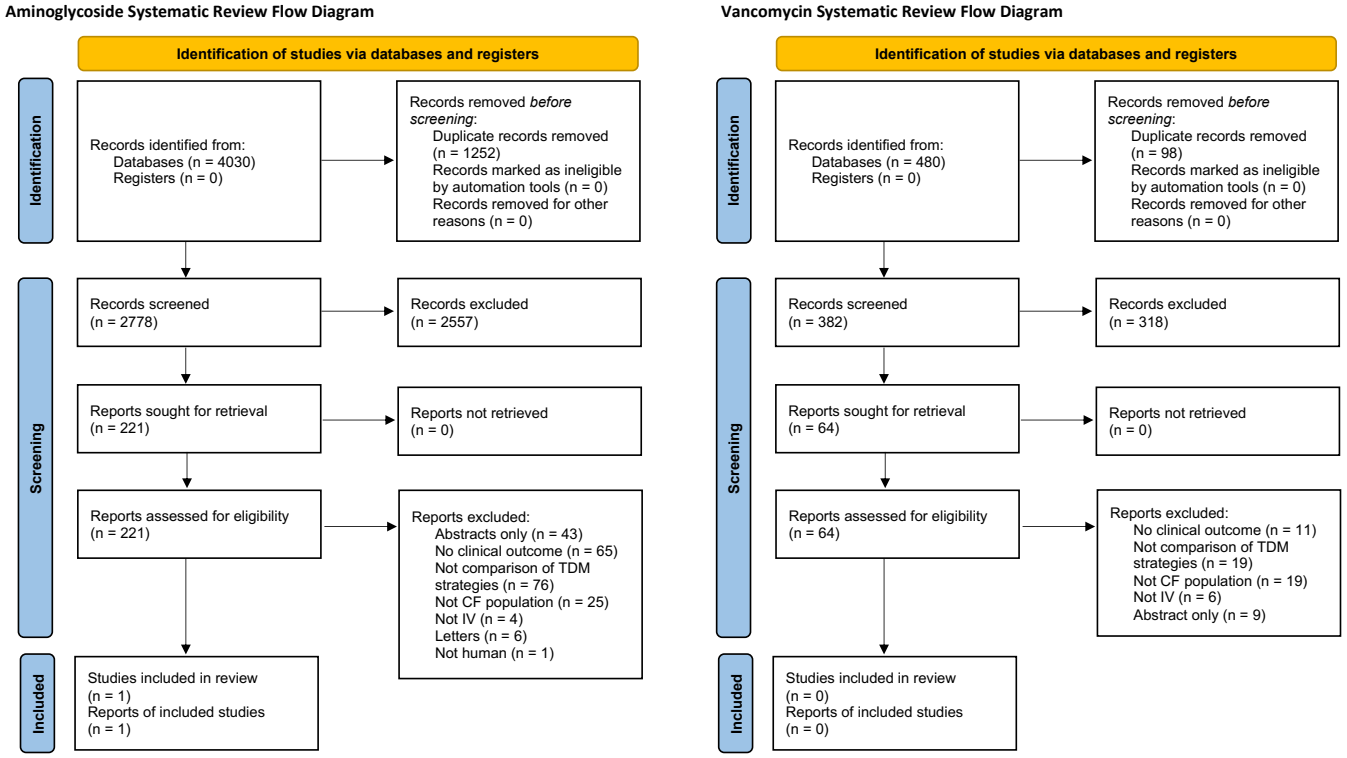

FIGURE 1. PRISMA flow diagram of study selection based on initial search, performed on November 15, 2020. CF = cystic fibrosis, TDM = therapeutic drug monitoring.

by dosing interval. This suggestion is congruent with the concentration-dependent antimicrobial activity of aminoglycosides[6] but was contradicted by the observed log–linear correlation between ppFEV$_1$ and C_{max}/MIC being lower than the correlation between ppFEV$_1$ and AUC$_{24}$/MIC.[18] Notably, some patients had improvement in FEV$_1$ despite low C_{max}/MIC and AUC$_{24}$/MIC, and these were excluded from the log–linear model.[18] Similarly, Landmesser and others[19] observed that more than 60% of patients had return to baseline FEV$_1$ despite not achieving C_{max} or AUC$_{24}$ targets; there was no statistical difference from patients who achieved these targets, but the study was likely not powered to detect such a difference. The AKI risk also was not correlated with AUC$_{24}$/MIC or C_{max}/MIC, but the risk increased with multiple daily doses relative to extended-interval dosing.[19] Exploratory analyses of a retrospective review evaluating the impact of aminoglycoside PK exposure on clinical outcomes in pwCF indicated that AUC and C_{max} were not associated with FEV$_1$ recovery, and no optimal threshold for either parameter was identified for this outcome.[22]

TABLE 1 (Part 1 of 2). Summary of Characteristics and Results of Included Studies for TDM Strategies in People with Cystic Fibrosis

Reference and Study Design	Population	Regimen	TDM Strategies Compared	Results
Aminoglycosides				
Burkhardt et al. (2006)[18] Single centre, open-label RCT	n = 33 adults, age range 19–37 years *Exclusions:* pre-existing renal insufficiency or hearing impairment; aminoglycoside or β-lactam hypersensitivity; pregnancy	Tobramycin 10 mg/kg divided q8h (n = 16) vs q24h (n = 17) × 14 days Target C_{tr} and C_{pk}: • q8h: < 2 mg/L, 5–20 mg/L • q24h: < 1 mg/L, 20–40 mg/L	C_{max}/MIC vs AUC$_{24}$/MIC	• Log–linear correlation between C_{max}/MIC and AUC$_{24}$/MIC with ppFEV$_1$ at 14 days (C_{max}/MIC: r^2 = 0.17 [q8h], 0.31 [q24h]; AUC$_{24}$/MIC: r^2 = 0.63 [q8h], 0.62 [q24h]) • For equal AUC$_{24}$/MIC value, better improvement in ppFEV$_1$ with q24h than with q8h dosing • C_{max}/MIC outcome not dependent on q24h vs q8h dosing • Toxicity not reported
Landmesser et al. (2021)[19] Retrospective chart review (Aug. 1, 2015, to Aug. 31, 2019)	n = 66 patients (151 encounters), age range 0.8–61 years • n = 19 pediatric patients (≥ 1 month old; 44 encounters) • n = 47 adult patients (107 encounters) *Exclusions: Pseudomonas aeruginosa* not identified in sputum culture; pre-existing CKD; 2 post-dose drug levels not obtained during admission, after ≥ 20% dose change, or after change in dose interval due to fluctuating renal function	Tobramycin • Dose adjusted to achieve calculated C_{tr} < 0.5 mg/L and C_{pk} ≥ 12 mg/L • 85% received q24h dosing	C_{max} (target ≥ 8× highest-documented MIC for *P. aeruginosa*) vs AUC$_{24}$ (target 80–120 mg*h/L)	• Of patient encounters in which AUC$_{24}$ was ≥ 80 mg*h/L or target C_{max} was achieved, absolute FEV$_1$, returned to baseline in 75.8% (p = 0.147) and 80.3% (p = 0.065), respectively • Difference in mean C_{max} and AUC$_{24}$ for patient encounters in which FEV$_1$ did and did not return to baseline was NSS • No association between increasing AUC$_{24}$ or C_{max} and development of AKI • Increased incidence of AKI with multiple daily doses vs extended-interval dosing (50% vs 29% of encounters, respectively; p = 0.047)
Hemmann et al. (2022)[20] Ambidirectional cohort study (June 1, 2018, to Feb. 8, 2021)	n = 53 pediatric patients (< 18 years), mean age 10.6 years *Exclusions:* did not receive monitoring per assigned cohort; second admission within 30 days of the previous admission	Tobramycin 10 mg/kg q24h or amikacin 30 mg/kg IV q24h • In intervention group, dose adjusted to achieve target C_{max}, C_{min}, and DFI	Control (cohort 1): trough-only monitoring (n = 21: June 1, 2018, to Feb. 28, 2019) Intervention (cohort 2): patient-specific PK calculations (n = 32: June 1, 2019, to Feb. 8, 2021) • levels measured 2 and 8 h post-dose • trough level used if no indication to repeat PK calculations[a]	• No difference in change in ppFEV$_1$ from admission to discharge between cohorts 1 and 2 (11.4% vs 13.9%; p = 0.55) • Difference in duration of antibiotics and length of stay NSS between cohorts 1 and 2 • Dose adjustment after initial level(s)[b]: 75% in cohort 2 vs 0% in cohort 1 (p < 0.001) • Nephrotoxicity (SCr 1.5× baseline): 6.3% in cohort 2[c] vs 0% in cohort 1 (NSS)

TABLE 1 (Part 2 of 2). Summary of Characteristics and Results of Included Studies for TDM Strategies in People with Cystic Fibrosis

Reference and Study Design	Population	Regimen	TDM Strategies Compared	Results
Vancomycin				
Mitchell et al. (2022)[21] Retrospective chart review (Oct. 1, 2015, to Jan. 31, 2021)	$n = 60$[d] (155 encounters), age range 0.25–55 years • $n = 26$ pediatric patients (42 encounters) • $n = 36$ adult patients (113 encounters) *Exclusions:* < 5 days of IV vancomycin during or after transplant	Initial dose per institutional policy, then adjusted to achieve TDM target	Trough-only monitoring (Oct. 1, 2015, to Oct. 1, 2018), target 10–20 mg/L AUC monitoring (Oct. 2, 2018, to Jan. 31, 2021), target 400–600 mg*h/L (calculated using 2-point estimate)	• Return to baseline $ppFEV_1$ for trough vs AUC monitoring in adults[e]: 56.5% vs 86.5% ($p = 0.002$) • Return to baseline $ppFEV_1$ for trough vs AUC monitoring in pediatric patients[f]: 80% vs 67% ($p = 0.458$) • Difference in median time to next exacerbation NSS between groups in adult or pediatric study populations • Median TDD for trough monitoring: adult 52 (IQR 42–70) mg/kg, pediatric 58 (IQR 55–70) mg/kg • Median TDD for AUC monitoring: adult 40 (IQR 34–54) mg/kg, pediatric 60 (IQR 54–72) mg/kg • Incidence of AKI NSS between trough and AUC monitoring, both overall (17% vs 12%, respectively; $p = 0.451$) and in adult and pediatric subgroups • Grade 2 and 3 AKI[g] in 1 adult each in trough-monitoring group; all other AKIs were grade 1[g]

AKI = acute kidney injury, AUC = area under the curve, AUC_{24} = area under the curve in 24 h, AUC_{24}/MIC = ratio of area under the curve in 24 h to minimum inhibitory concentration, CFTR = cystic fibrosis transmembrane conductance regulator, CKD = chronic kidney disease, C_{max}/MIC = ratio of maximum concentration to minimum inhibitory concentration, C_{max} = maximum concentration, C_{min} = minimum concentration, C_{pk} = peak concentration, C_{tr} = trough concentration, DFI = drug-free interval, FEV_1 = forced expiratory volume in 1 second, IQR = interquartile range, MIC = minimum inhibitory concentration, NSS = not statistically significant, PK = pharmacokinetic, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second, RCT = randomized controlled trial, SCr = serum creatinine, TDD = total daily dose, TDM = therapeutic drug monitoring.

[a]Patient-specific PK calculations were completed at least once every 6 months for admitted patients, sooner if patient had any of the following criteria: ≥ 30% change in SCr, ≥ 20% change in weight, significant change in fluid status, or admission to pediatric intensive care unit.[20]

[b]Change in dose after initial measurement of aminoglycoside serum concentration(s) was the primary outcome of this study.[20]

[c]The 2 patients who experienced SCr 1.5× baseline were receiving concurrent nephrotoxic medications and had a history of SCr elevations while receiving aminoglycosides.

[d]The total numbers of adult and pediatric patients sum to 62 but represent only 60 unique individuals, as 2 patients had admissions included in both the pediatric and adult cohorts.[21]

[e]Of adult patients in the trough- and AUC-monitoring groups with return to baseline FEV_1, 20% and 50%, respectively, were receiving concomitant CFTR modulator therapy.[21]

[f]Of pediatric patients in the trough- and AUC-monitoring groups with return to baseline FEV_1, 75% and 58%, respectively, were receiving concomitant CFTR modulator therapy.[21]

[g]Per Kidney Disease Improving Global Outcomes (KDIGO) criteria.[21]

Concerns have been raised about observed increases in *P. aeruginosa* MIC with extended-interval dosing, potentially because of the prolonged drug-free interval[18]; the majority of dose adjustments in the study by Hemmann and others[20] were in order to shorten the drug-free interval, but this did not result in better clinical outcomes. Moreover, antimicrobial sensitivity testing does not reliably predict clinical outcomes in pwCF.[23]

The aforementioned findings raise the question: Is aminoglycoside TDM strategy or dosing regimen more important for clinical outcomes? The available literature suggests that extended-interval dosing maximizes C_{max}/MIC and the post-antibiotic effect, while decreasing risk for AKI.[10,12]

Vancomycin

Although the study results suggest greater return to baseline $ppFEV_1$ among adults with AUC-based monitoring than those with trough-based monitoring, the disproportionate number of patients who were receiving CFTR modulators is a potential confounder.[21] The relatively smaller disparity

in CFTR modulator use and higher baseline ppFEV$_1$ among pediatric patients may account for the lack of observed difference between the study groups.[21]

Mitchell and others[21] did not report whether the difference between groups in vancomycin total daily dose was statistically significant. However, the decrease in total daily dose for adults in the AUC-based monitoring group and lower troughs observed in the AUC-based monitoring group overall may translate to clinical benefit, given the evidence suggesting that AKI risk with vancomycin increases with higher troughs and AUC.[14]

Limitations

The primary limitation of this systematic review was the small number of studies that met the inclusion criteria. This likely reflects a lack of studies evaluating these outcomes in pwCF, as we utilized a robust search strategy in multiple databases and reviewed the grey literature to minimize the risk of publication bias. The potential for selection bias was addressed by having 2 reviewers independently screen for and identify eligible studies. No studies were excluded as a result of the TDM strategy being non-reproducible. All included studies had a small sample size, which limited generalizability as well as statistical power to detect outcome differences. Moreover, 3 of the 4 studies involved retrospective analysis of data, which carries an intrinsic risk for confounding variables. There were insufficient data from the included studies to evaluate optimal TDM targets in pwCF.

CONCLUSION

Available evidence is insufficient to determine an optimal TDM strategy for IV aminoglycosides or IV vancomycin in pwCF. Prospective randomized controlled trials (RCTs) are required to better evaluate the correlation of aminoglycoside AUC_{24}/MIC and C_{max}/MIC with clinical outcomes in pwCF, as well as to elucidate the impact of conventional versus extended-interval dosing. Similarly, RCTs are required to compare the clinical outcomes of different vancomycin TDM strategies in pwCF. Future studies involving pwCF should also explore whether optimal TDM strategy varies by age group and should focus on determining optimal TDM targets. In the era of highly effective CFTR modulators, achieving the necessary sample size to evaluate these outcomes may prove difficult; therefore, it is imperative that the CF community collaborate in attempts to fill these important gaps in the literature.

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