Optimal Therapeutic Drug Monitoring and Sampling Strategies for IV Aminoglycosides and IV Vancomycin in Cystic Fibrosis: A Systematic Review

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Background

- People with cystic fibrosis (pwCF) have frequent acute pulmonary exacerbations (APE) requiring IV antibiotics
- Aminoglycosides (AMG) and vancomycin are commonly-used IV antibiotics and require therapeutic drug monitoring (TDM)
- There is no consensus for TDM strategies in pwCF receiving IV AMG or IV vancomycin
- Alternative sampling strategies for AMG or vancomycin TDM that optimize comfort in pwCF has not been summarized
- Our objective was to determine if there is an optimal TDM and sampling strategy for pwCF receiving IV AMG or IV vancomycin

Methods

- **Design**: Systematic review, PROSPERO CRD42020212941
- **Databases (searched Nov 15, 2021)**: MEDLINE, Embase, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov
- **Inclusion**: pwCF receiving IV AMG or IV vancomycin for APE, clinical outcomes as primary endpoint (for TDM strategies)
- **Exclusion**: Insufficient detail about TDM strategy and PD parameter targeted, *in vitro* or non-human, study abstract
- **Screening**:-Two independent reviewers
- **Risk of bias**: National Heart, Lung, and Blood Institute (NIH) risk assessment tool; two independent reviewers

Table 1: PICO Questions

	TDM STRATEGY		SAMPLING STRATEGY	
	AMG	Vancomycin	AMG	Vancomycin
Intervention	- PD/TDM strategies		- Alternative sampling sites	
Comparator	- Peak and trough level	- Trough level only	- Peripheral venipuncture	
Primary Outcomes	- Lung function - Toxicity		- Level accuracy - Error rate	

Legend for Tables 2-3

AUC:MIC	Ratio of area under the curve to minimum inhibitory concentration
C_{max}:MIC	Ratio of maximum concentration to minimum inhibitory concentration
CVC	Central venous catheter
PICC	Peripherally inserted central catheter

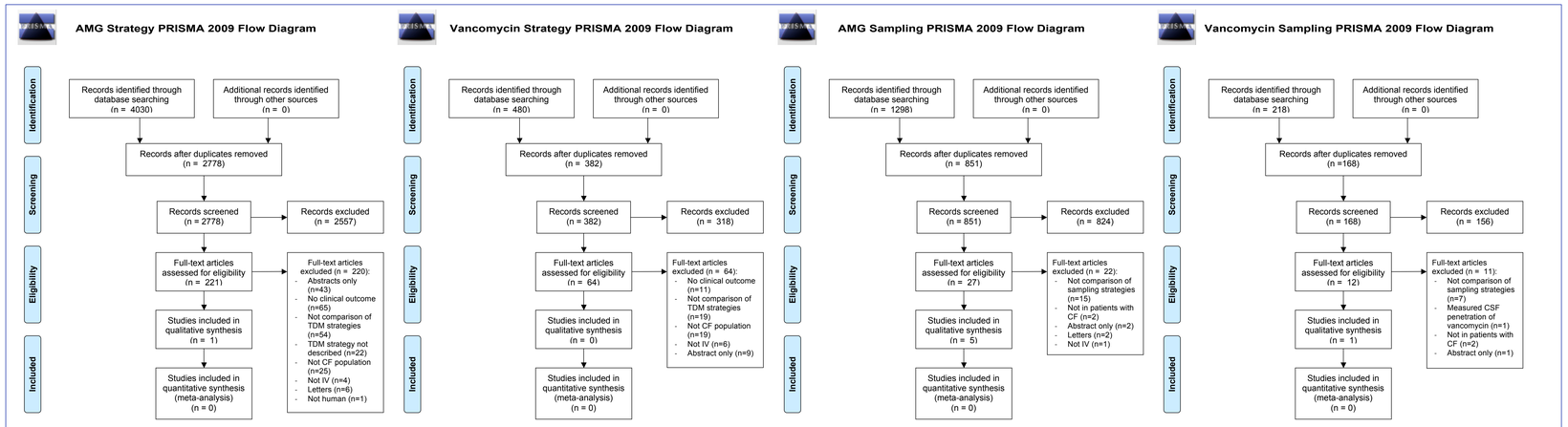

Figure 1: PRISMA Flow Diagrams

Results – Relevant Studies

Table 2: Aminoglycoside TDM Strategy Results

Author & Design	Participants & AMG Regimen	Intervention & Comparator	Results
Burkhardt 2006 Single centre, open-label RCT	n=33 adults with CF Tobramycin 10mg/kg/day div q8h vs q24h x 14 days	C_{max}:MIC vs. AUC:MIC	- Correlation between C_{max}:MIC and AUC:MIC - Cmax:MIC unaffected by dosing regimen - MIC increased by average 6.8mg/L with q24h dosing (unchanged for q8h) - Toxicity not reported

Table 3: Aminoglycoside and Vancomycin Sampling Results

Author	Participants & Antibiotic	Intervention & Comparator	Accuracy	% Error
Jones 2012	- n=54 adults - Tobramycin	Finger prick vs. peripheral venipuncture	Bland-Altman analysis bias: - Trough -0.03mg/L - Peak 0.38mg/L	Trough = 2.7% Peak = 0%
Madsen 2004	- n=14 children - Tobramycin	Saliva vs. peripheral venipuncture	All saliva samples undetectable	N/A
McBeth 2004	- n=23 children - Tobramycin (n=86 samples)	CVC/PICC (5mL flush, 5mL discard) vs. peripheral venipuncture	**1h post-infusion**: CVC 24% higher than peripheral (t= -2.49, p=0.017) **3h post-infusion**: CVC 10% higher than peripheral (t= -2.26, p=0.029)	10/85 = 11.6%
Mogayzel 2008	- Children - Tobramycin **Phase 1**: n=19 (n=53 samples) **Phase 2**: n=20 (n=30 samples)	CVC vs. peripheral venipuncture **Phase 1**: 3mL flush, 3mL discard **Phase 2**: 10-20mL flush, 3mL discard	**Phase 1**: median CVC 39% higher than peripheral **Phase 2**: median CVC 8% higher than peripheral	Phase 1: 43% Phase 2: 13%
Wilson 2012	- n=38 children - Tobramycin and vancomycin	CVC (5mL flush, 5mL discard) vs. peripheral venipuncture or finger prick	**Tobramycin**: - Trough r=0.65, p=0.012 - Peak r=0.93, p<0.001 **Vancomycin**: - Trough r=0.59, p=0.043	Tobra: 0% Vanco: 15%

Conclusions

Aminoglycoside TDM strategy:

- Insufficient evidence to support one strategy over another.
  - Peak- and trough-based TDM most common
  - C_{max}:MIC may correlate with clinical efficacy better than AUC:MIC

Vancomycin TDM strategy:

- No studies identified in pwCF

Sampling site strategies:

- Finger prick and CVC samples may be considered
  - Higher CVC flush volumes may improve accuracy (may depend on CVC type)

Gaps in research:

- Prospective trials in pwCF comparing clinical outcomes of TDM strategies for IV AMG and IV vancomycin
- Comparison of specific CVC types and flush regimens