CLINICAL INVESTIGATION

Tobramycin and Beta-Lactam Antibiotic Use in Cystic Fibrosis Exacerbations: A Pharmacist Approach

Jeffery T. Zobell, PharmD,¹ Kevin Epps, PharmD,² Frederick Kittell, PharmD,³ Clarissa Sema, PharmD,⁴ Erin J. McDade, PharmD,⁵ Stacy J. Peters, PharmD,⁶ Mariela A. Duval, PharmD,⁷ and Rebecca S. Pettit, PharmD, MBA⁸

¹Intermountain Primary Children's Hospital, Salt Lake City, Utah; ²St. Vincent's Hospital Riverside, Jacksonville, Florida; ³University of Wisconsin Hospital, Madison, Wisconsin; ⁴University of Arizona, Tucson, Arizona; ⁵Texas Children's Hospital, Houston, Texas; ⁶Sanford Medical Center, Sioux Falls, South Dakota; ⁷Children's Healthcare of Atlanta, Atlanta, Georgia; ⁸Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana

OBJECTIVES: Survey suggests that recommended doses and dosage regimens for antipseudomonal antibiotics for the treatment of acute pulmonary exacerbations in cystic fibrosis (CF) patients are not used, and one way to address these disparities is the involvement of pharmacists who are dedicated to CF. This is the first survey specifically designed for pharmacists at Cystic Fibrosis Foundation (CFF)-accredited centers to identify how tobramycin and antipseudomonal beta-lactams are being used. The purpose of this survey is to quantify this information and to promote future study to allow for implementation of tobramycin and beta-lactam dosage and monitoring standardization.

METHODS: An anonymous national cross-sectional survey of pharmacists that are affiliated with CFF-accredited programs was performed using Qualtrics.com.

RESULTS: The survey had a 48.5% response rate. Most pediatric pharmacists (78.6%) report using extended-interval tobramycin dosage. The most common reported starting dosage was 10 mg/kg every 24 hours; most centers aim for a maximum serum concentration (C_{max}) between 20 and 40 mg/L (78.6%). A total of 26 adult pharmacists reported using extended-interval dosage (96%), using an initial dosage of 10 mg/kg/day. The most common parameters used to adjust dosage were C_{max} and area under the curve (AUC; 31%); the C_{max} goal was 20 to 40 mg/L (84.2%). Most respondents (79%) report using beta-lactams in combination with tobramycin. Extended-infusion and continuous-infusion beta-lactams were used more in adults than pediatric patients.

CONCLUSIONS: Most CF pharmacists report using extended-interval tobramycin. With the information from this survey, the establishment of future consensus recommendations by pharmacists for optimal and consistent tobramycin and antipseudomonal beta-lactam dosage and monitoring strategies needs to be considered.

INDEX TERMS: aminoglycosides, antibiotics, antipseudomonal, beta-lactam, cystic fibrosis, extended-interval dosage, pediatrics, pharmacokinetics, pulmonary exacerbations, survey, tobramycin

J Pediatr Pharmacol Ther 2016;21(3):239–246

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a defective chloride transport channel in multiple organ systems, including the lungs and gastrointestinal tract.^{1–3} Detrimental effects of thick, dehydrated secretions, bacterial infections, and inflammation result in bronchiectasis and progressive obstructive airway disease.^{1–3} Acute pulmonary exacerbations (APEs) are managed with either oral, aerosolized antibiotics (mild exacerbations) or with intravenous

antibiotics (moderate to severe exacerbations), which can be administered in the hospital and/or at home.^{1–3}

In 2009, the Cystic Fibrosis Foundation (CFF) released guidelines for the treatment of APEs.⁴ These guidelines recommend that APEs be treated with two intravenous antipseudomonal antibiotics, each with a different mechanism of action, in an effort to enhance antibacterial activity and reduce resistance.⁴ According to recent surveys, the most commonly used intravenous antipseudomonal antibiotic classes were

beta-lactams (98%) and aminoglycosides (61%-94.3%).⁵⁻⁷ These surveys also elicited interesting results regarding the dosage strategies currently used by care centers.⁵⁻⁷

Previous surveys of CF centers revealed that recommended doses and dosage regimens are not used by a substantial number of CF centers despite CFF, European, and UK CF Trust Working Group recommendations, and literature confirming the efficacy and safety of larger than Food and Drug Administration–approved doses for beta-lactam agents and once-daily aminoglycosides.⁸⁻¹⁰ Possible explanations may include concern for dose-related adverse effects incurred from larger doses, lack of familiarity with dosage guidelines among CF practitioners, lack of understanding of fundamental pharmacokinetic/pharmacodynamics principles, lack of a dedicated CF pharmacist, and the use of published dosage references which do not contain these doses.⁵⁻⁷ These surveys suggest that additional education and implementation strategies are needed to assist CF practitioners in optimizing the treatment of APEs.

One way that may aid in addressing these concerns is the involvement of pharmacists who are specifically dedicated to CF. According to a European Consensus statement and the United Kingdom CF Trust Standard, pharmacists are considered primary members of the multidisciplinary CF care team with specific duties.^{11,12} One of these duties is to individualize drug and dosage requirements (e.g., optimization of medications through maximizing therapeutic benefit and minimizing toxicity; therapeutic drug monitoring of aminoglycosides and vancomycin based on individual patient pharmacokinetic parameters).^{11,12}

Pharmacists play a key role in recommending and monitoring antibiotics for the treatment of APE, which may aid in the optimization of dosage strategies. However, there is no standardization of dosage and monitoring across the United States. The CFF guidelines recommend the use of once-daily aminoglycosides but do not provide recommendations for initial dosage for all age groups, timing of serum concentrations, frequency of serum concentrations, or other monitoring recommendations. A survey of US CF center directors reported 61 US CF centers having a dedicated CF pharmacist.¹³ This is the first survey specifically designed for pharma-

cists at CFF-accredited centers to identify how tobramycin and antipseudomonal beta-lactams are being used via dosage regimens as well as monitoring strategies. This survey will help assess if the involvement of a pharmacist helps assist with the literature-based dosage and use of tobramycin in CF patients. Information from this survey will promote future study and allow for the standardization of tobramycin and beta-lactam dosage and monitoring.

METHODS

An anonymous, Institutional Review Board–approved, national, cross-sectional survey of pharmacists affiliated with CFF-accredited pediatric and/or adult programs was performed using Qualtrics.com (Provo, UT).

The questions were developed by a group of 7 CF pharmacists. This survey was designed to quantify different strategies for dosage and monitoring of both beta-lactams and tobramycin. These questions were then piloted to a small group and modified before the final survey was released. Pharmacists affiliated with CFF-accredited pediatric and/or adult programs were identified if they attended the North American Cystic Fibrosis Conference or are members of the CF Pharmacy CFF-sponsor ListServ.

RESULTS

Pediatric Tobramycin Use

A total of 68 pharmacists were contacted and 33 pharmacists responded, for a response rate of 48.5%. A total of 28 CF pharmacists, each from a different CF center in the United States, answered the survey questions regarding the use of tobramycin in pediatric patients. All responding pediatric pharmacists reported routinely using tobramycin in their pediatric patients with CF. Of those 28, a total of 78.6% reported using extended-interval dosage of tobramycin most commonly, whereas 6 pharmacists reported still using standard-interval (every 8 hours) dosage. Of all survey responders, most respondents reported using extended-interval tobramycin dosage in all patients older than 1 month (Table 1). Survey results for tobramycin use and dosage in pediatric and adult patients with CF are summarized in Tables 2 and 3. Information on standard dosage in pediatric patients with CF is

Table 1. Percent Use of Extended-Interval Tobramycin Dosage by Age Group

Patient Age	No. (%) of Respondents Using Extended-Interval Tobramycin (n = 28)
Neonate (age <1 mo)	11 (39.3)
Infant (age 1-12 mo)	23 (82.1)
Young children (age 1-5 yr)	26 (92.9)
Older children (age 6-12 yr)	27 (96.4)
Adolescent (age 13 to <18 yr)	27 (96.4)

depicted in Table 4.

Of the pharmacists using extended-interval tobramycin, the most common initial extended-interval tobramycin dosage used was 10 mg/kg per dose every 24 hours (72.7%), followed by 11 to 12 mg/kg per dose every 24 hours (27.3%). The maximum dose given when using extended-interval dosage ranged from 12 to 20 mg/kg per dose. All respondents reported monitoring tobramycin serum concentrations, with the most common monitoring strategy involving two randomly collected concentrations (72.7%). The next most common monitoring strategy was the use of a peak and trough concentration (13.6%). The maximum concentration ($C_{\max}$) and area under the curve (AUC) were the most commonly used parameters to individualize tobramycin dosage. The most common goals were $C_{\max}$ of 20 to 40 mg/L (78.6%) and goal AUC of 80 to 120 mg*hr/L (80%). Subsequent follow-up monitoring of tobramycin concentration involved a trough concentration drawn every 7 days (54.5%).

Centers using standard-interval tobramycin dosage reported that the most common dosage was 3 to 3.5 mg/kg given every 8 hours (83.3%). The most common approach to monitor dosage in pediatric patients used peak and trough serum concentrations (66.7%) that were back-extrapolated $C_{\max}$ to a target concentration within the range of 8 to 20 mg/L. Follow-up peak and trough serum concentration were most commonly obtained every 7 days.

Adult Tobramycin Use

A total of 27 pharmacists answered the survey questions related to tobramycin use in adults with CF. A total of 26 pharmacists (96%) working with adult patients reported using extended-interval dosage, with only 1 respondent reporting the use of standard-interval dosage. A total of 19 respondents (73%) reported using an initial dose

age of 10 to 12.5 mg/kg per dose every 24 hours, whereas 5 pharmacists (11.5%) reported using an initial dose <10 mg/kg. Administration time was also requested, with 14 pharmacists (53.8%) reporting a 60-minute infusion and the remaining pharmacists using a 30-minute infusion (Table 3).

All respondents reported collecting tobramycin serum concentrations to monitor therapy, with the most common being two random concentrations (76.9%), followed by peak and trough (7.7%), single random concentration (7.7%), and trough only (7.7%). Of the 26 responses, the most common parameters used to adjust dosage were $C_{\max}$ and AUC (31.8%), $C_{\max}$ only (31.8%), and peak and trough serum concentrations (9%). Two respondents answered that they did not use any parameters, one respondent reporting using AUC only, and another reported using $C_{\max}$ plus post antibiotic effect time to adjust tobramycin dosing. Goals for $C_{\max}$ with extended-interval dosage varied, but the most common response was 20 to 30 mg/L (52.6%), followed by 30 to 40 mg/L (21.1%). When all responses were compiled, including free text entries, 16 pharmacists (84.2%) reported using a goal $C_{\max}$ between 20 and 40 mg/L. Those using AUC to guide dosage noted most frequently that 80 and 125 mg*hr/L were the lower and upper limits, respectively. Similarly to pediatrics, follow-up tobramycin serum concentrations were most commonly obtained every 7 days.

Antipseudomonal Beta-lactam Use

Most of the survey participants (79%) reported using combination antibiotics to treat APE. The most common beta-lactam antibiotics used in pediatric patients included ceftazidime (89%), piperacillin/tazobactam (78%), meropenem (63%), cefepime (48%), and ticarcillin/clavulanate (33%). Twenty-seven responders (79%) also use beta-lactam antibiotics in combination with tobramycin in adult patients, with the most com-

Table 2. Data Regarding Extended-Interval Dosage of Tobramycin in Adult and Pediatric Patients

Question (No. of Respondents)	Responses (%)		
	Most Common	2nd Most Common	3rd Most Common
Do you use extended interval dosing?			
Adult (n = 27)	Yes (96.3)	No (3.7)	N/A
Pediatric (n = 28)	Yes (78.6)	No (21.4)	N/A
What duration of infusion is used?			
Adult (n = 26)	60 min (53.8)	30 min (46.2)	N/A
Pediatric (n = 22)	30 min (72.7)	60 min (27.3)	N/A
What initial dose is used?			
Adult (n = 26)	10 mg/kg (50)	10-12.5 mg/kg (23.1)	<10 mg/kg (19.2)
Pediatric (n = 26)	10 mg/kg (72.7)	11-12 mg/kg (27.3)	N/A
What is the maximum dose used?			
Adult (n = 17)	12 mg/kg (29.4); 14-15 mg/kg (29.4)	10 mg/kg (17.6); no max noted (17.6)	8 mg/kg (5.9)
Pediatric (n = 17)	12 mg/kg (17.6)	14, 15, 20 mg/kg (11.6)	10 (5.9); 14-15 (5.9); 15 (5.9); or 600 mg (5.9); 15-16 (5.9); 16 (5.9); 18 mg/kg (5.9); no stated max (5.9)
What initial dosing frequency is used?			
Adult (n = 26)	Every 24 hr (88.5)	Every 18 or 18-24 hr (7.7)	Every 12 hr (3.9)
Pediatric (n = 22)	Every 24 hr (81.8)	Every 12 hr (9.1)	Every 18 hr (4.5)

N/A, not applicable

mon antibiotics being piperacillin/tazobactam (85%), meropenem (78%), ceftazidime (74%), cefepime (52%), and aztreonam (26%). When asked about laboratory parameters used to monitor for possible adverse reactions due to the combination antibiotic regimen, adult centers monitored basic metabolic panel (i.e., Na, K, Cl, CO₂, blood urea nitrogen [BUN], serum creatinine, glucose, Ca) more often than pediatric centers (85% vs. 67%), but both reported similar incidence for complete blood count and liver function tests (52% and 41%, respectively, for adult and pediatric patients). The most common method for beta-lactam administration in pediatric patients was intermittent dosage (70% vs. 52% in adults). Conversely, the use of continuous infusion of the beta-lactam occurred more often in adults (41% vs. 30% in pediatric). Only 2 adult centers (7%) indicated commonly using continuous infusion of beta-lactams, and none of the pediatric center responders indicated using continuous infusion as their most common duration of administration.

DISCUSSION

To our knowledge, this study represents the first attempt to quantify aminoglycoside and antipseudomonal beta-lactam use in CF pulmonary exacerbations from the pharmacist's perspective. Tobramycin was chosen in place of other antipseudomonal aminoglycosides (i.e., gentamicin and amikacin) because it has been reported in previous surveys to be the most commonly used treatment for CF patients (61%-98.5%).^{6,7} Studies have shown that extended-interval (i.e., once daily) tobramycin is a safe and effective alternative to traditional (i.e., every 8 hours) tobramycin dosage.¹⁴⁻¹⁹ The results of our survey are consistent with these findings that 80% of pediatric and 96% of adults centers reporting use of extended-interval tobramycin. The most frequently used initial dosage of tobramycin for extended-interval therapy in both adult and pediatric patients was 10 mg/kg per dose every 24 hours. This dosage strategy is consistent with guideline recommendations from the UK and

Table 3. Monitoring of Extended-Interval Dosage of Tobramycin in Adult and Pediatric Patients

Question (No. of Respondents)	Most Common	Responses (%) 2nd Most Common	3rd Most Common
Do you monitor serum tobramycin concentrations?			
Adult (n = 26)	Yes (100)	No (0)	N/A
Pediatric (n = 22)	Yes (100)	No (0)	N/A
What tobramycin concentrations are measured?			
Adult (n = 26)	Two random concentrations (76.9)	Peak and trough (7.7)	N/A
Pediatric (n = 22)	Two random concentrations (72.7)	Peak and trough (13.6)	Trough only (9.1)
If two random concentrations are measured: What is the timing of two random concentrations?			
Adult (n = 19)	2 hr (26.3)	8 hr (21.1)	10 hr (8.4)
Pediatric (n = 16)	2 hr (50)	8 hr (22.7)	10 hr (18.2)
What pharmacokinetic parameters are calculated to adjust dosing?			
Adult (n = 22)	C_{max} and AUC (31.8)	C_{max} only (31.8)	Other (36.4)
Pediatric (n = 22)	C_{max} and AUC (31.8)	C_{max} only (27.3)	Peak and trough, trough only (9.1)
At what time point do you define of C_{max} ?			
Adult (n = 22)	At the end of infusion (46.7)	30 min after end of infusion (40)	Other (13.3)
Pediatric (n = 13)	30 min after end of infusion (61.5)	At the end of infusion (38.5)	N/A
If C_{max} calculated, what is your goal extrapolated C_{max} ?			
Adult (n = 19)	20-30 mg/L (52.6)	30-40 mg/L (21.2)	25-35 mg/L (10.5); 16-24 mg/L (10.5)
Pediatric (n = 14)	20-40 mg/L (35.7)	20-30 mg/L (28.6)	10-20, 30-40 mg/L (14.3)
If AUC is calculated: what is your goal AUC?			
Adult (n = 8)	80-120 mg*hr/L; 80-125 mg*hr/L; 70-125 mg*hr/L (25)	N/A	70-100, 60-120 mg*hr/L (12.5)
Pediatric (n = 5)	80-120 mg*hr/L (80)	75-125 mg*hr/L (20)	N/A
What is the accepted duration of drug free period before dose modification?			
Adult (n = 18)	Not calculated (27.8)	8, 10, 12 hr (16.7)	6 hr (11.1)
Pediatric (n = 20)	Not calculated (35)	8, 10, 12 hr (15)	6 hr (10)
How frequently are serum concentrations drawn following attainment of a "therapeutic" dose?			
Adult (n = 19)	Every 7 days (57.9)	Based on clinical judgment (26.3)	Every 3 days (10.5)
Pediatric (n = 22)	Every 7 days (54.5)	Based on clinical judgment (18.2)	Every 3 days (9.1)
What specific concentrations are drawn as follow-up after attainment of a therapeutic dose?			
Adult (n = 19)	Two random concentrations, trough only (42.1)	N/A	Single random concentration (15.8)
Pediatric (n = 21)	Trough concentration only (47.6)	Two random concentrations (28.6)	Single random concentration at 18 hr (9.5)
What laboratory tests are used to aid in monitoring adverse effects			
Adult (n = 18)	Basic metabolic panel (72.2)	BUN and serum creatinine (61.1)	CBC with differential (33.3)
Pediatric (n = 22)	Basic metabolic panel (63.6)	BUN and serum creatinine (59.1)	CBC with differential (18.2)

AUC, area under the curve; BUN, blood urea nitrogen; C_{max} , maximum serum concentration; CBC, complete blood count; N/A, not applicable

Table 4. Data Regarding Standard-Interval Dosage (2.5 mg/kg Every 8-12 hr) of Tobramycin in Pediatric Patients

Question (No. of Respondents)	Responses (%)		
	Most Common	2nd Most Common	3rd Most Common
Do you use traditional dosing (n = 28)	No (78.6)	Yes (21.4)	N/A
What traditional dose do you use? (n = 6)	3-3.5 mg/kg per dose (83.3)	2-2.5 mg/kg per dose (16.7)	N/A
What traditional dosing frequency do you use? (n = 6)	every 8 hr (83.3)	Every 12 hr (16.7)	N/A
What duration of infusion is used? (n = 6)	30 min (83.3)	60 min (16.7)	N/A
Do you monitor serum tobramycin concentrations? (n = 6)	Yes (100)	N/A	N/A
What pharmacokinetic parameters are calculated to adjust dosing? (n = 6)	Extrapolated C_{max} only (66.7)	Extrapolated peak and trough (33.3)	N/A
What is your extrapolated C_{max} goal? (n = 6)	Goal not specified (33.3)	8-10 (16.7); 10-12 (16.7); 12-15 (16.7); 15-20 mg/L (16.7)	N/A
How do you define C_{max} ? (n = 6)	At the end of the infusion (66.7)	30 min after the end of the infusion (16.7)	60 min after the end of the infusion (16.7)
How frequently are tobramycin concentrations drawn following attainment of a therapeutic dose? (n = 6)	Every 7 days (66.7)	Based on clinical judgment (33.3)	N/A
What specific concentrations are drawn as follow-up after attainment of a therapeutic dose? (n = 6)	Peak and trough (88.3)	Two random concentrations (16.7)	N/A
What laboratory tests are used to aid in monitoring adverse effects of traditional dosing? (n = 6)	Basic metabolic panel and BUN and serum creatinine (66.7)	Basic metabolic panel (16.7)	Basic metabolic panel, BUN and serum creatinine; CBC with differential; and liver function tests (16.7)

BUN, blood urea nitrogen; CBC, complete blood count; C_{max} , maximum serum concentration; N/A, not applicable

CFF as well as the published literature.^{4,10,20}

Existing literature does not provide recommendations regarding the best time to obtain serum concentrations, the frequency of serum concentration monitoring, or other monitoring (e.g., BUN, serum creatinine) recommendations. With the lack of standardized monitoring recommendations, respondents reported several different strategies for monitoring the safe and effective use of tobramycin. The most common strategy reported was to check two random serum concentrations (73%; i.e., 2 hours and 8 hours), which would then be used to calculate C_{max} and AUC. These two pharmacokinetic parameters have been shown to correlate with improvements in lung function (i.e., forced expiratory volume in 1

second, forced vital capacity).^{14,21,22} Most pediatric and adult survey respondents reported a goal C_{max} that ranged between 20 and 40 mg/L, trough serum concentrations <1 mg/L, and AUC ranges of 70 to 125 mg*hr/L, which are consistent with literature recommendations.^{14-17,19,20-22}

Follow-up monitoring of serum concentrations differed between pediatric and adult respondents. Pediatric respondents measured only trough concentrations every 7 days, whereas most adult respondents measured 2 random serum concentrations every 7 days. Most respondents noted that laboratory monitoring of renal function, liver function, and blood cell counts were routinely assessed.

The majority of pediatric and adult respondents

(79% for both) reported using antipseudomonal beta-lactams in combination with tobramycin for the treatment of APEs. This is comparable to previous studies, where 96% to 98% of all respondents reported using antipseudomonal beta-lactams in the treatment of APEs.^{5,7} The most commonly used beta-lactams reported were ceftazidime, piperacillin-tazobactam, meropenem, and cefepime, which are consistent with a previous survey.⁵ The use of extended-infusion beta-lactam was also consistent with the rate reported in the study by Zobell and colleagues.⁵

A limitation of the study is the survey response rate of approximately 50% of identified pharmacists affiliated with CFF-accredited care centers. Because half of the pharmacists did not respond, the response rate may limit the generalizability of the study results. However, the response rate is comparable to previous antibiotic use surveys (42%-46%).⁵⁻⁷

CONCLUSION

In conclusion, this survey describes the previously unknown prevalence of use, dosage, and monitoring strategies of tobramycin and antipseudomonal beta-lactam among pharmacists in the United States who provide care to patients with CF. Variance does exist in the dosage and monitoring strategies of tobramycin, but based on the most common responses and literature recommendations, tobramycin may be initially dosed using an extended interval of 10 mg/kg/day every 24 hours. Serum tobramycin concentrations should be measured to meet monitoring parameters of $C_{\max}$ (range, 20-40 mg/L), serum trough concentration <1 mg/L, and AUC range 70 to 125 mg*hr/L. Antipseudomonal beta-lactams may be administered via intermittent infusion or extended infusion when given in combination with tobramycin. With the information from this survey, the establishment of future consensus recommendations by pharmacists for optimal and consistent tobramycin and antipseudomonal beta-lactam dosage and monitoring strategies needs to be considered.

Disclosure The author(s) declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Acknowledgments Steven Tran, PharmD, St. Vincent's Hospital Riverside, for assistance in aggregating survey data. This work was previously presented as a poster at the 2014 North American Cystic Fibrosis Conference.

Abbreviations APE, acute pulmonary exacerbation; AUC, area under the curve; BUN, blood urea nitrogen; CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; $C_{\max}$, maximum concentration

Correspondence Rebecca S. Pettit, PharmD, MBA, BCPS, Riley Hospital for Children at Indiana University Health, 705 Riley Hospital Dr. SFTW6111, Indianapolis, IN 46202; email: rpettit1@iuhealth.org

REFERENCES

1. Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med*. 1996;335(3):179-188.
2. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med*. 2003;168(8):918-951.
3. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176(10):957-969.
4. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med*. 2009;180(9):802-808.
5. Zobell JT, Young DC, Waters CD, et al. A survey of the utilization of antipseudomonal beta-lactam therapy in cystic fibrosis patients. *Pediatr Pulmonol*. 2011;46:987-990.
6. Van Meter DJ, Corriveau M, Ahern JW, Lahiri T. A survey of once-daily dosage tobramycin therapy in patients with cystic fibrosis. *Pediatr Pulmonol*. 2009;44(4):325-329.
7. Prescott WA Jr. National survey of extended-interval aminoglycoside dosing in pediatric cystic fibrosis pulmonary exacerbations. *J Pediatr Pharmacol Ther*. 2011;16(4):262-269.
8. Cystic Fibrosis Foundation. *Microbiology and infectious disease in cystic fibrosis: Cystic Fibrosis Consensus Conference May 17-18, 1994*. Vol. 5. Bethesda, MD: Cystic Fibrosis Foundation; 1994:section 1:1-26.

9. Doring G, Conway SP, Heijerman HGM, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. *Eur Respir J*. 2000;16(4):749-767.
10. UK Cystic Fibrosis Trust. Antibiotic treatment for cystic fibrosis in UK Cystic Fibrosis Trust Antibiotic Working Group. 2009. <https://www.cysticfibrosis.org.uk/~media/documents/the-work-we-do/care/consensus-documents/antibiotic-treatment-cystic-fibrosis-may-09.ashx?la=en>. Accessed May 19, 2016.
11. UK Cystic Fibrosis Trust, Cystic Fibrosis Pharmacists Steering Group. Pharmacy standards in cystic fibrosis care. 2011. <https://www.cysticfibrosis.org.uk/~media/documents/the-work-we-do/care/consensus-documents/pharmacy-standards-of-care-nov-11.ashx?la=en>. Accessed May 19, 2016.
12. Conway S, Balfour-Lynn IM, De Rijcke K, et al. European cystic fibrosis society standards of care: framework for the cystic fibrosis centre. *J Cyst Fibros*. 2014;13(suppl 1):S3-S22.
13. Bhakta ZN, Young DC, Zobell JT, et al. A survey of the pharmacist's role at US CFF-accredited centers-a director's perspective. *Pediatr Pulmonol*. 2013;48(S36):39.
14. Burkhardt O, Lehmann C, Madabushi R, et al. Once-daily tobramycin in cystic fibrosis: better for clinical outcome than thrice-daily tobramycin but more resistance development? *J Antimicrob Chemother*. 2006;58(4):822-829.
15. Vic P, Ategbro S, Turck D, et al. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Arch Dis Child*. 1998;78(6):536-539.
16. Whitehead A, Conway SP, Etherington C, et al. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis. *Eur Respir J*. 2002;19(2):303-309.
17. Master V, Roberts GW, Coulthard KP, et al. Efficacy of once-daily tobramycin monotherapy for acute pulmonary exacerbations of cystic fibrosis: a preliminary study. *Pediatr Pulmonol*. 2001;31(5):367-376.
18. Riethmueller J, Ballmann M, Schroeter TW, et al; German Multicenter Study Group. Tobramycin once- vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. *Infection*. 2009;37(5):424-431.
19. Smyth A, Tan KH, Hyman-Taylor P, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial. *Lancet*. 2005;365(9459):573-578.
20. Young DC, Zobell JT, Stockmann C, et al. Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: V: aminoglycosides. *Pediatr Pulmonol*. 2013;48(11):1047-1061.
21. Aminimanizani A, Beringer PM, Kang J, et al. Distribution and elimination of tobramycin administered in single or multiple daily doses in adult patients with cystic fibrosis. *J Antimicrob Chemother*. 2002;50(4):553-559.
22. Mouton JW, Jacobs N, Tiddens H, Horrevorts AM. Pharmacodynamics of tobramycin in patients with cystic fibrosis. *Diagn Microbiol Infect Dis*. 2005;52(2):123-127.