TITLE: Inhaled Tobramycin versus Intravenous Tobramycin for Patients with Cystic Fibrosis: A Review of the Clinical Effectiveness, Cost Effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

The defective cystic fibrosis transmembrane conduction receptor (CFTR) gene in patients with cystic fibrosis (CF) leads to an increased production of mucus in many organs in the body, in particular a build-up of thickened mucus in the lungs, leading to chronic pulmonary infection.[1] The management of bacterial pneumonia in patients with CF is usually challenging due to difficult-to-eradicate gram negative bacilli as common etiological agents in this group.[1] Tobramycin, a water-soluble aminoglycoside, has been proved to be effective in the management of bacterial pneumonia infection due to gram-negative bacilli such as *Pseudomonas aeruginosa* (PA).[1] Despite intravenous (IV) tobramycin having been used widely for the eradication of PA, the well-known toxicities of IV aminoglycosides to the kidneys, hearing loss, and toxicity to the vestibular system are concerns.[2] Inhaled tobramycin was developed to target infected airways efficiently, while limiting systemic exposure and toxicity,[3-6] and has been shown to improve health outcomes in CF patients.[7-13] Inhaled tobramycin which includes tobramycin inhalation solution (TIS) (Tobi; Novartis Pharmaceuticals Canada Inc.) and the recently developed tobramycin inhalation powder (TIP or Tobi Podhaler; Novartis Pharmaceuticals Canada Inc.) were approved by Health Canada in 2006 and 2011, respectively, for the treatment of *Pseudomonas aeruginosa* lung infection in patients with CF.[14]

This report aims to provide a review on the comparative clinical and cost-effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) and IV tobramycin for the treatment of patients with CF. The evidence on the compliance rate of patients with CF taking inhaled tobramycin or IV tobramycin will also be reviewed. Evidence-based guidelines regarding the use of tobramycin for the treatment of patients with CF will be reported.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) versus IV tobramycin sulfate solution for the treatment of patients with CF?

2. What is the comparative cost effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) versus IV tobramycin sulfate solution for the treatment of patients with CF?

3. What is the evidence of the compliance rate of patients with CF taking Tobi, Tobi Podhaler or IV tobramycin sulfate solution?

4. What are the evidence-based guidelines regarding the use of tobramycin for the treatment of patients with CF?

KEY FINDINGS

No evidence was identified comparing the clinical and cost effectiveness of inhaled tobramycin to IV tobramycin in the treatment of CF patients. A nephrotoxicity study of tobramycin on CF patients found that long-term use of neither inhaled nor IV tobramycin was associated with a decline in kidney function. Adherence rates with inhaled tobramycin were low. Despite no association found between inhaled tobramycin adherence and the frequency of pulmonary exacerbation, compared to patients with high adherence with inhaled tobramycin, those using less than 4 cycles of TIS per year were more likely to be hospitalized. Guidelines from the CF Foundation recommended that alternate month tobramycin solution for inhalation should be used chronically for infants who remain infected with PA after two attempts at eradication. Guidelines recommend chronic use of inhaled tobramycin to improve lung function and reduce exacerbations in patients with CF 6 years of age and older with chronic *Pseudomonas aeruginosa* infection.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including MEDLINE, EMBASE, PubMed, The Cochrane Library (2012, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1998 and January 15, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Patients with CF
Intervention	Tobi (inhaled tobramycin sulfate solution) Tobi Podhaler (inhaled tobramycin powder)
Comparator	IV tobramycin sulfate solution
Outcomes	Clinical efficacy Cost effectiveness Compliance rate Guidelines and Recommendations
Study Designs	Health technology assessments, systematic reviews, meta-analyses and guidelines. If no systematic reviews were identified, randomized controlled trials (RCTs), and non-RCTs were selected for inclusion.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 1998, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included non-randomized studies, and guidelines was assessed using Downs and Black,[15] and AGREE[16] checklists, respectively.

Numeric scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 527 citations. Three additional studies were identified by searching the grey literature or hand searching. After screening of abstracts, 41 potentially relevant studies were selected for full-text review.

After full-text screening, three studies[17-19] and two guidelines[20,21] met the inclusion criteria and were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection. Additional citations of potential interest which did not meet the inclusion criteria are provided in Appendix 2.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 3.

Study design

This report included three retrospective studies that looked at the safety of inhaled or IV tobramycin,[17] and adherence with inhaled tobramycin.[18,19] Two evidence-based guidelines were included.[20,21]

Population

The toxicity study included 113 adult CF patients (mean age 31.7).[17] The studies on adherence with inhaled tobramycin included 804 CF patients of all ages,[18] and 95 CF patients ≥6 years of age.[19] One guideline was for infants under two years of age with CF.[20] The second guideline provided recommendations for patients with CF 6 years of age or older.[21]

Interventions and comparators

The toxicity study examined the nephrotoxicity of IV tobramycin, colistin, gentamycin, or vancomycin, and inhaled tobramycin, colistin, or gentamycin.[17] The adherence studies looked at patients' adherence with inhaled tobramycin,[18] azithromycin, dornase alfa, hypertonic saline and inhaled tobramycin.[19] The guidelines looked at all types of management for patients with CF, including antibiotics for PA.[20,21]

Outcomes

The toxicity study looked at renal toxicity as measured by BUN (blood urea nitrogen), creatinine.[17] The adherence studies measured the adherence to inhaled tobramycin, health care utilization,[18] and association of adherence with health outcomes.[19] Outcomes of the guidelines review are recommendations for the management of infants with CF,[20] or individuals at least 6 years of age.[21]

Summary of Critical Appraisal

In general, the included studies had hypotheses, main interventions and outcomes clearly described. The included studies are retrospective in design with its inherent limitations, including risk of selection bias and lack of blinding. The occurrence of toxicities episodes could not be documented systematically in a retrospective way.[17] The adherence studies used measures that reflected medication acquisition rather than medication use.[18,19] In general, one guideline review provided specific and unambiguous recommendations, but many of the recommendations were based on expert consensus due to lack of evidence.[20] The second guideline[21] was based on a systematic review of the evidence, with recommendations developed by an expert committee representing relevant clinical specialties such as nursing, pediatrics, internal medicine, and respiratory therapy. Recommendations in this guideline were clear and unambiguous, with each recommendation assigned a grade based on strength of evidence and estimate of net benefit, however costs do not appear to have been considered in the recommendations.[21] This guideline stated that recommendations will be amended as new data are reported, but a process for updating the guideline was not provided.[21] Potential conflicts of interest were clearly stated, with

some members declaring financial relationships with commercial entities with an interest in the subject of the guidelines.

Details of the strengths and limitations of the included studies are summarized in Appendix 4.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 5.

1. What is the comparative clinical effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) versus IV tobramycin sulfate solution for the treatment of patients with CF?

The literature search did not identify any study comparing the clinical effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) versus IV tobramycin sulfate solution for the treatment of patients with CF.

One retrospective study examined the toxicity of long-term use of IV and inhaled nephrotoxic antibiotics on the renal function of patients with CF.[17] Adult patients (n = 113) with chronic use of IV tobramycin, colistin, gentamycin, or vancomycin and inhaled tobramycin, colistin or gentamycin were followed up for a maximum of 8.5 years. Renal function was determined by changes in blood urea nitrogen (BUN) and creatinine following treatment. IV tobramycin use after a mean of 62.7 days did not correlate with a statistically significant change in BUN or creatinine (the same effect was seen with IV colistin, gentamycin, or vancomycin). Inhaled tobramycin use after a mean of 166.5 days also did not correlate with a statistically significant change in BUN or creatinine [inhaled colistin and gentamycin use was associated with a statistically significant change in BUN, but only inhaled colistin was associated with acute kidney injury (defined as an acute increase of serum creatinine greater than 1.2 mg/dL)].

2. What is the comparative cost effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) versus IV tobramycin sulfate solution for the treatment of patients with CF?

The literature search did not identify any study comparing the cost effectiveness of inhaled tobramycin (Tobi and Tobi Podhaler) versus IV tobramycin sulfate solution for the treatment of patients with CF.

3. What is the evidence of the compliance rate of patients with CF taking Tobi, Tobi Podhaler or IV tobramycin sulfate solution?

Two studies examined the compliance rate of patients with CF using inhaled tobramycin and its relationship with health care utilization and clinical outcomes.[18,19] In general, among patients with CF and a prescription for TIS, only 7% were categorized as having high adherence with TIS, while high adherence with TIS was associated with a decreased risk of hospitalization when compared to patients with lower adherence rate. There was, however, no association found between TIS adherence with the occurrence and frequency of a pulmonary exacerbation, or a decline in lung function.

A retrospective study based on a research database of health care claims of 804 patients with CF[18] determined adherence to TIS as measured by the number of TIS therapy cycles completed in a year. Adherence was categorized as low (≤2 cycles per year), medium (>2 to <4 cycles per

year) and high (≥4 cycles per year). 72% of patients were ranked as having low, 22% having medium and 7% having high adherence. Compared to patients with high adherence with TIS, those using less than 4 cycles per year were more likely to be hospitalized (41% vs 26%). Probability calculations showed that the odds of hospitalization was 60% less in patients with high adherence with TIS compared to those with low adherence.

A retrospective study of 95 CF patients[19] examined medication adherence of azithromycin, dornase alfa, hypertonic saline, and inhaled tobramycin (TIS or TIP not specified) as measured by medication possession ratio (MPR) which is the ratio between the sum of the number of days the medication was received and the number of days the medication was prescribed in 12 months. The mean MPR for inhaled tobramycin was 65% and the composite MPR (for all the studied medications) was 63%. While composite MPR was associated with the occurrence of at least one pulmonary exacerbation requiring a course of IV antibiotic treatment, inhaled tobramycin MPR was not associated with the frequency of pulmonary exacerbations or a decline in lung function (determined as reduction of forced expiratory volume in 1 second or FEV1). Dornase alfa MPR and inhaled tobramycin MPR were the only drugs that predicted baseline FEV1.

4. What are the evidence-based guidelines regarding the use of tobramycin for the treatment of patients with CF?

The CF Foundation commissioned an evidence review from Johns Hopkins University regarding identification of issues in the care of infants with CF, and development of evidence-based recommendations in 2009.[20] Regarding the use of tobramycin for the treatment of PA infections, the review recommended that alternate month tobramycin solution for inhalation should be used chronically for infants who remain infected with PA after two attempts at eradication.

The evidence review stated under Recommendations 32 through 34 (pS76, Table 1):

> *32 For infants with CF under two years of age, the CF Foundation recommends against the use of chronic antibiotics for prophylaxis to prevent Pseudomonas aeruginosa*
> *Certainty: Low; Benefit: Zero-negative* (benefit is defined as estimate of net benefit, which is benefit minus harm)
> *Consensus recommendation*
>
> *33 For infants with CF under two years of age, the CF Foundation recommends that new acquisition of Pseudomonas aeruginosa, defined as initial acquisition or new acquisition after 'successful' eradication therapy, should be treated with anti-pseudomonal antibiotics and increased airway clearance, regardless of the presence or absence of symptoms.*
> *Certainty: Low; Benefit: Moderate*
> *Consensus recommendation*
>
> *34 For infants with CF under two years of age, the CF Foundation recommends that infants who remain persistently colonized with Pseudomonas aeruginosa after two attempts at eradication be treated chronically with alternate month tobramycin solution for inhalation*
> *Certainty: Low; Benefit: Moderate*
> *Consensus recommendation (pS76)*[20]

The Cystic Fibrosis Foundation also established a committee to examine the clinical evidence for different CF therapies and to provide guidance to physicians for the prescription of these treatments.[21] These guidelines were published in 2007.[21] Regarding the use of tobramycin for

the suppression of chronic *Pseudomonas aeruginosa* infection, the following recommendations were made:

> *"For patients with CF, 6 years of age and older, who have moderate to severe lung disease and with P. aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations. Level of evidence, good; net benefit, substantial; grade of recommendation, A" (p.958)*
>
> *"For patients with CF, age 6 years and older who are asymptomatic or with mild lung disease, and with P. aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations. Level of evidence, fair; net benefit, moderate; grade of recommendation, B" (p. 959)*

The committee further concluded that there was insufficient evidence to recommend for or against routine provision of other inhaled antibiotics.[21]

Limitations

The limited number of studies included in the review and their retrospective design caution the interpretation of the findings. There were no studies on comparative clinical and cost effectiveness between inhaled and IV tobramycin that would have facilitated the decision on the use of these two approaches. Findings on adherence rates are limited as the studies on adherence used pharmacy refill records which reflect an assessment of medication acquisition rather than medication use. There were no studies identified on adherence with IV tobramycin. Recommendations in one included guideline[20] were largely based on expert consensus due to lack of evidence. These recommendations were focused on infants under 2 years of age, and may not be generalizable to a broader population. A second guideline[21] provided recommendations for patients aged 6 years or older, however it did not appear to consider IV administration of tobramycin and no recommendations were provided in that regard. Recommendations were not based on a specific tobramycin formulation, and recommended doses were not provided. Furthermore the guidelines were based on literature published between 1983 and 2006 and may not be reflective of more recent research or newer products such as tobramycin inhalation powder.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There no evidence comparing the clinical and cost effectiveness of inhaled tobramycin to IV tobramycin in the treatment of CF patients. Long-term use of neither inhaled nor IV tobramycin was associated with a decline in kidney function in CF patients. Adherence rate with inhaled tobramycin was low. Despite no association found between inhaled tobramycin adherence and the frequency of pulmonary exacerbation, low adherence was associated with increased risk of hospitalization. Guidelines from the CF Foundation recommended that alternate month tobramycin solution for inhalation should be used chronically for infants who remain infected with PA after two attempts at eradication. Guidelines recommend chronic use of inhaled tobramycin to improve lung function and reduce exacerbations in patients with CF aged 6 years and older with mild or moderate to severe lung disease and chronic *Pseudomonas aeruginosa* infection.

An RCT comparing the effect of inhaled tobramycin and a combination of IV tobramycin and IV ceftazidine on lung infection in CF children with PA infection was identified.[22] This study was not

included in the summary of findings because the efficacy of the intervention (a combination of IV tobramycin plus IV ceftazidine) cannot be attributed to IV tobramycin alone. Lung inflammation, determined by neutrophil profile in bronchoalveolar lavage fluids (BALF), showed that the IV treatment group had a statistically significant greater reduction in total white blood cells and polymorphonuclear cell counts in BALF than the inhaled tobramycin group. Because of the paucity of the evidence comparing IV to inhaled antibiotics in CF patients, findings from this randomized trial can be one factor to consider for health care professionals. Detailed findings of this study were summarized in Appendix 6.

Among studies of TIS for CF, the comparative efficacy between the 80mg twice daily continuous treatment (Tiv 80) and 300mg twice daily (Tis 300) in cycles of 28 days on and 28 off treatment for a total period of 24 weeks was studied in an underpowered RCT that found differences in lung functions were not statistically significant between the two dosages.[23] However, this finding should be interpreted with caution as the trial included a power calculation to determine appropriate sample sizes for treatment groups, but failed to recruit the required number of participants to detect clinically important effects with statistical significance.[23] Individual preferences indicated that patients preferred the high-dose inhalation cycle compared to the lower dose continuous inhalation.[23] An RCT comparing the safety, efficacy and convenience of TIS (Tobi) and tobramycin inhalation powder (TIP) found that both have similar safety and efficacy profiles, but the powder inhalation form required much less time to administer (mean 5.6 min vs 19.7 min; $P < 0.0001$) leading to better patient treatment satisfaction.[24]

There was no evidence found on the comparative cost-effectiveness of inhaled tobramycin and IV tobramycin, but there was one cost study identified that evaluated the economic impact of TIS in the care of CF patients.[25] The study retrospectively examined medical and pharmacy claims data of TIS users and non-TIS users for CF. Compared to non-TIS users, total costs and CF-related PMPM (per-member-per-month) costs in users decreased 17% and 3%, respectively. Increase in TIS prescription costs was found to be off-set by decrease in patient costs in this study. It is important to note that, with the large variation in management approach for CF, the “non-TIS users” cannot serve as a real comparator group compared to the TIS-users group. Findings from this study agreed with a budget impact analysis of TIS that compared TIS treatment + standard care with standard care alone over a 4-year time horizon.[26] Baseline characteristics of the two treatment groups were similar (patients in the standard care group used their routine medication with no other inhaled antibiotics; 39% of the patients in the TIS + standard care group received IV antibiotics compared to 52% in the standard care alone group). Assuming an increase of TIS utilization from 20% to 25% (based on current TIS utilization of 20% within the US CF eligible population) over 1 year, this resulted in a smaller increase in overall budget as compared with the increase in net drug budget, due to a decrease in hospitalization rate and a decrease in IV anti-PA antibiotic administration. This translated in a medical care cost saving of US$ 50,676 over 4 years per patient (costs reported in 2008 US dollars). However, this model, like most models, was based on a number of assumptions, including the combination of two IV anti-PA antibiotics for 14 days in an event of an acute pulmonary exacerbation, and on the assumption that the adherence to treatment is perfect and constant duration the study period. More details of the budget impact results were summarized in Appendix 7.

More randomized controlled trials are needed to provide strong evidence to form guidelines and recommendations on the use of inhaled tobramycin and IV tobramycin, as well as on different dosage options of antibiotics for CF patients.

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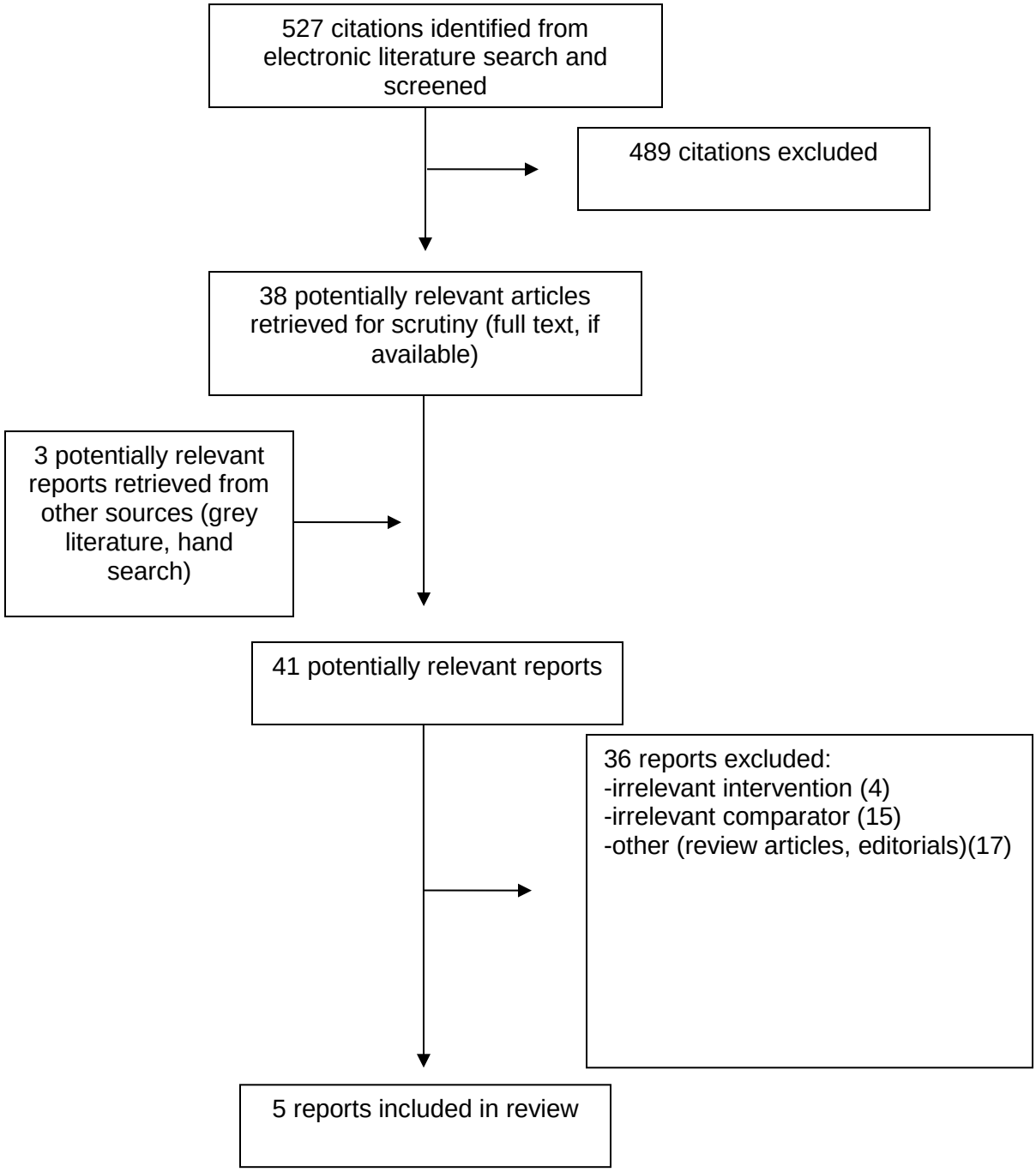
Appendix 1: Selection of Included Studies



Appendix 2: Additional Studies of Potential Interest

Review articles (Not systematic)

Pai VB, Nahata MC. Efficacy and safety of aerosolized tobramycin in cystic fibrosis. Pediatr Pulmonol. 2001 Oct;32(4):314-27.
PubMed: PM11568993

Economic Evaluations of Inhaled Tobramycin (IV tobramycin not considered)

Iles R, Legh-Smith J, Drummond M, Prevost A, Vowler S. Economic evaluation of Tobramycin nebuliser solution in cystic fibrosis. J Cyst Fibros. 2003 Sep;2(3):120-8.
PubMed: PM15463860

LeLorier J, Perreault S, Birnbaum H, Greenberg P, Sheehy O. Savings in direct medical costs from the use of tobramycin solution for inhalation in patients with cystic fibrosis. Clin Ther. 2000 Jan;22(1):140-51.
PubMed: PM10688397

Appendix 3: Characteristics of Included Studies

Table A1: Characteristics of Included studies

First Author, Year, Country,	Study objectives	Intervention Comparator(s)	Included patients and study types	Main clinical outcomes reported
Florescu,[17] 2012 US	"*We studied the impact of chronic nephrotoxic antibiotic exposure on kidney function in CF population*" (p 414)	IV tobramycin, colistin, gentamycin, or vancomycin Inhaled tobramycin, colistin,or gentamycin	113 adult CF patients (mean age 31.7; SD = 9.9) Retrospective study	Renal toxicity (BUN, creatinine)
Briesacher,[18] 2011 US	To determine adherence with tobramycin inhaled solution (TIS) and health care utilization	TIS	804 CF patients (of all ages) Retrospective study, using pharmacy claim records	Adherence to TIS utilization (measured as the number of therapy cycles completed per year) Health care utilization
Eakin,[19] 2011 US	"*This study examined the relationship of medication adherence to frequency of pulmonary exaxerbation and rate of decline in FEV1% predicted*" (p 258)	Azithromycin, dornase alfa, hypertonic saline, inhaled tobramycin.	95 CF patients ages 6 years or older Retrospective study, using pharmacy claim records	Adherence (MPR) Association between adherence and health outcome (pulmonary exacerbations as determined by requirement of a course of IV antibiotics; decline of FEV1)
Borowitz,[20] 2009 US	"*These guidelines…are intended to help guide families, primary care providers, and specially care centers in the care of infants*" (p S73)	Not applicable	Infants with CF Evidence-based guidelines	Recommendations
Flume,[21] 2007 US	"*To provide guidance to the physician who must choose from an ever-expanding arsenal of treatments for chronic CF lung disease"* (p. 957)	Not applicable	Individuals at least 6 years of age Evidence-based guidelines	Recommendations

BUN: blood urea nitrogen; CF: cystic fibrosis; FEV1: forced expiratory volume in 1 second; IV: intravenous; MPR: medication possession ratio; SD: standard deviation

Appendix 4: Summary of Critical Appraisal of Included Studies

Table A2: Summary of Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Florescu,[17] 2012	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described	• retrospective design • characteristics of patients lost to follow-up were not described • unclear whether study had sufficient power to detect a clinically important effect
Briesacher,[18] 2011	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described	• retrospective design • losses to follow-up not described • estimates of random variability and actual probability values not provided • unclear whether study had sufficient power to detect a clinically important effect
Eakin,[19] 2011	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described	• retrospective design • characteristics of patients lost to follow-up were not described • unclear whether study had sufficient power to detect a clinically important effect
Borowitz,[20] 2009	• Scope and purpose of the guidelines are clear • The recommendations are specific and unambiguous • Target users of the guideline are clearly defined • The guideline was piloted among target users • References are provided for the recommendations • Guideline development group includes individuals from all the relevant professional groups	• Much of the recommendations is based on expert consensus due to lack of evidence • Unclear whether patients' views and preferences were sought • Unclear whether the guideline was reviewed externally prior to publishing • Potential cost implications of applying the recommendation were not included in the recommendation
Flume,[21] 2007	• Scope and purpose of the guidelines are clear • The recommendations are specific and unambiguous • Target users of the guideline are clearly defined • Recommendations are based on a systematic review of the evidence • Guideline development group includes individuals from all the relevant professional groups	• Unclear whether patients' views and preferences were sought • Potential cost implications of applying the recommendation were not included in the recommendation • A procedure for updating the guideline was not provided

Appendix 5: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness of inhaled tobramycin vs intravenous tobramycin)		
Florescu,[17] 2012	**Renal toxicity** IV tobramycin: use of IV tobramycin did not correlate with changes in BUN (p = 0.51) or creatinine (p = 0.17) Inhaled tobramycin: use of inhaled tobramycin did not correlate with changes in BUN (p = 0.17) or creatinine (p = 0.58)	IV tobramycin and inhaled tobramycin were not associated with impaired renal function of patients with CF
Research question 2 (cost effectiveness of inhaled tobramycin vs intravenous tobramycin)		
The were no studies identified for this research question		
Research question 3 (evidence of the compliance rate of inhaled tobramycin and intravenous tobramycin)		
Briesacher,[18] 2011	**Adherence to TIS** Number of TIS therapy cycles completed per year Low utilization (≤2 cycles): 71% Medium utilization (>2 to <4 cycles): 22% High utilization (≥4 cycles): 7% **Health care utilization** Percentage of patients hospitalized Low utilization (≤2 cycles): 42.9% Medium utilization (>2 to <4 cycles): 40.6% High utilization (≥4 cycles): 25.9% Risk of hospitalization (AOR) Low utilization: 1.0 (reference) Medium utilization: 0.94 (95% CI 0.62 to 1.41) High utilization:0.40 (95% CI 0.19 to 0.84)	"*among 804 individuals identified with CF and a prescription for TIS, only 7% received ≥4 cycles of TIS per year. High adherence with TIS was associated with a decreased risk of hospitalization when compared to individuals receiving ≤2 cycles*" (p 1)
Eakin,[19] 2011	**Adherence to azithromycin, dornase alfa, hypertonic saline and inhaled tobramycin** (median MPR) Inhaled tobramycin: 65% Azithromycin: 76% Dornase alfa: 90% Hypertonic saline: 25% Composite: 63% **Association between adherence and pulmonary exacerbations** (IV antibiotics requirement) **and pulmonary function** (FEV1) Dornase MPR and inhaled tobramycin MPR predicted baseline FEV1, but not a decline in FEV1 No association between lower inhaled tobramycin MPR with the frequency of a pulmonary exacerbation Composite MPR predicted baseline FEV1, but not a decline in FEV1	There was no association between adherence to inhaled tobramycin with pulmonary exacerbations or decline in lung function in CF patients.

AOR: adjusted odds ratio; BUN: blood urea nitrogen; CF: cystic fibrosis; FEV1: forced expiratory volume in 1 second; IV: intravenous; MPR: medication possession ratio; PA: pseudomonas aeroginosa; TIS: tobramycin inhaled solution;

Appendix 6: Findings and Authors' Conclusions in RCT comparing inhaled tobramycin with a combination of IV antibiotics[22]

Table A4: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Noah,[22] 2010	Change in % BALF neutrophils Inhaled group: +5.4, 95% CI -11 to 15 Systemic group: -7.4, 95% CI -35 to 0 *p* = 0.07 Changes in BALF total cells count/ml² Inhaled group: -3% Systemic group: -50% *p* < 0.01 Changes in BALF PMN/ml² Inhaled group: -10% Systemic group: -74% *p* = 0.02 Change in BALF PA cfu/ml (thousands) Inhaled group: pre-treatment: 10; post-treatment: 2.5 Systemic group: pre-treatment: 6; post-treatment: 0 *p* = 0.22 Change in BALF all pathogens cfu/ml (thousands) Inhaled group: pre-treatment: 60; post-treatment: 2.5 Systemic group: pre-treatment: 15; post-treatment: 0 *p* = 0.45	"*In clinically stable children with CF, systemic antibiotics result in greater short-term reduction in lower airways inflammation than inhaled antibiotics*" (p 281)

BALF: bronchoalveolar lavage fluid; CF: cystic fibrosis; cfu: colony-forming unit; PMN: polymorphonuclear leukocytes; PA: pseudomonas aeruginosa; RCT: randomized controlled trial.

Appendix 7: Budget impact results of increasing use of TIS in CF patients[26]

Table A5: Budget impact results					
	Current utilization	Year 1	Year 2	Year 3	Year 4
Estimated TIS utilization	20%	25%	30%	35%	40%
Number of patients treated with TIS	44	54	65	76	87
Total hospitalizations	153	152	151	150	149
Total IV anti-PA treatments	167	165	164	162	161
Total drug budget	$1,088,216	$1,332,136	$1,576,055	$1,819,975	$2,063,894
Drug budget impact relative to budget of current year	n/a	$243,919	$487,839	$731,758	$975,678
Overall budget impact relative to budget of current year	n/a	$231,251	$462,501	$693,752	$925,002

n/a: not applicable; CF: cystic fibrosis; TIS: tobramycin inhaled solution.