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THE DECISION-TREE MODEL IN PHARMACOECONOMIC ANALYSIS OF SHORT-TERM ANTIBIOTICS VERSUS STANDARD COURSE OF ORAL PENICILLIN IN TREATING CHILDREN WITH ACUTE STREPTOCOCCAL PHARYNGITIS

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Annotation. This article presents the results of the cost-effectiveness analysis of using short-term treatment with azithromycin, clarithromycin, cefuroxime and amoxicillin/clavulanate compared to standard 10-day course of oral penicillin in treating children with acute streptococcal pharyngitis. It was found, that the cost-effectiveness ratio (CER) of 5-day course of clarithromycin was 50% lower than CER of standard treatment with oral penicillin.
Keywords: pharyngitis/drug therapy, pharyngitis/economics, Streptococcus pyogenes, child.

Acute streptococcal pharyngitis is a common disease of the upper respiratory tract [1], late diagnosis and inadequate treatment of which may cause the development of early suppurative (peritonsillar abscess, cervical lymphadenitis, acute otitis media, mastoiditis, acute sinusitis) and late non-suppurative (acute rheumatic fever, acute poststreptococcal glomerulonephritis, rheumatic heart disease and poststreptococcal reactive arthritis) complications [2].

The basis for the treatment of acute streptococcal pharyngitis has been recognized to be antibacterial chemotherapy for eradication of the causative agent. It leads to reducing the severity and duration of clinical manifestations of infection, prevents poststreptococcal complications and infection spreading [3].

"Gold-standard treatment" of acute streptococcal pharyngitis is penicillin due to its clinical effectiveness, narrow bacteriological spectrum, relative safety and low cost [4].

It is known that Streptococcus pyogenes is completely sensitive to penicillin. Resistance has not developed to penicillin [2].

However, data on bacteriological treatment failure to penicillin (Streptococcus pyogenes eradication is asent) appeared in the literature. It can be caused by poor patient adherence to medication, synthesis of β-lactamase concomitant pharynx microflora, poor penetration of antibiotics into the focus of infection, etc [5].

It was found, that 10-day course of treatment is not completed by not all patients. Most patients consider taking antibiotics after the first 2-3 days against the backdrop of improving health and the absence of symptoms unnecessary [6]. According to this reason the scientific priority remains the research for antibiotics capable for the shorter term to ensure the same results as the 10-day course of oral penicillin.

The limited financial resources for health care are another important reason that motivates researchers to seek rational approaches to antimicrobial therapy. Based on the saving state budget and personal funds, essential part of patient pharmaceutical provision is pharmacoeconomic analysis that compares costs and outcomes between the standard and alternative treatment scheme.

Objective: to compare cost-effectiveness evaluation of using short duration treatment with azithromycin, clarithromycin and oral cefuroxime with standard 10-day course of oral penicillin in treating children with acute streptococcal pharyngitis.

Materials and methods. The object of pharmacoeconomic assessment was results of comparative prospective randomized controlled multicenter clinical trials comparing short duration oral antibiotics azithromycin (20 mg/kg), clarithromycin (7.5 mg/kg) and cefuroxime (10 mg/kg) to standard 10-day duration oral penicillin in children with acute streptococcal pharyngitis [7, 8, 9].

The decision-tree model was used to select the most effective and the least costly treatment approach. The essence of this method is to compare the likelihood of Streptococcus pyogenes eradication and economic costs for each of the compared approaches. Add-in PrecisionTree for Microsoft Excel, which has been developed by Palisade Corporation, was used to build the decision-tree model.

The effectiveness of treatment was estimated based on the criteria for achieving eradication of Streptococcus pyogenes on the posterior pharyngeal wall and tonsils in the first two weeks after completion of antibiotic treatment and absence bacteriological recurrence beyond the 4-6-week period after completion of pharmacotherapy.

The economic analysis implied the calculation of the direct medical costs for antibacterial treatment. The cost of pharmacotherapy was determined based on the retail price of a child's dosage form of the drug-brand. As the drug-brands of oral penicillin, clarithromycin and azithromycin are not registered in Ukraine, the on-line resource Drugs.com was the drug price database of all studied antibiotics [10].

The pharmacoeconomic analysis was conducted from a patient-payer's perspective. Horizon of modeling equals to duration course of acute streptococcal pharyngitis treatment.

Results and discussion.

Clinical evaluation. Quantitative assessment of clinical effect was measured with the odds ratio (OR) in the systematic review Cochrane [11]. Results of clinical trials indicated, that the risk of early bacteriological treatment failure was significantly reduced in the short duration treatment of clarithromycin (OR 0.22, 95% CI 0.12 to 0.41), azithromycin (OR 0.33, 95% CI 0.14 to 0.76) and oral cefuroxime (OR 0.59, 95% CI 0.43 to 0.82) compared to recommended standard 10-day duration of oral penicillin [11]. Than the odds ratio was less the probability of early bacteriological treatment failure after short-term treatment lower.

There was no significant difference in the risk of late bacteriological recurrence between of short-duration antibiotics and recommended standard duration of oral penicillin [11]. Detailed estimation of clinical trials is presented in the Table 1.

Clinical evaluation of short-term course chemotherapy of acute streptococcal pharyngitis in children

Interventions	Odds Ratio [M-H, Fixed, 95% CI]		Source
	Early bacteriological treatment failure	Late bacteriological recurrence	
Penicillin V 13.3 mg/kg three times a day for 10 days versus Clarithromycin 7.5 mg/kg twice a day for 5 days	0.22 [0.12, 0.41]*	1.08 [0.66, 1.75]**	[8]
Penicillin V 15 mg/kg three times a day for 10 days versus Azithromycin 20 mg/kg daily for 3 days	0.33 [0.14, 0.76]*	1.14 [0.55, 2.39]**	[7]
Penicillin V 30 mg/kg three times a day for 10 days versus Cefuroxime axetil 10 mg/kg (max 500 mg) twice a day for 5 days	0.59 [0.43, 0.82]*	0.81 [0.57, 1.14]**	[9]
Penicillin V 30 mg/kg three times a day for 10 days versus Amoxicillin/clavulanate 43.8/6.2 mg/kg/day (max 1 g) twice a day for 5 days	0,94 [0.49, 1.84]**	0,70 [0.37, 1.32]**	[15]

* Significant differences between groups, p <0.05
** No significant difference between groups, p> 0.05

Economic evaluation. Cost-minimization analysis showed that among pediatric dosage forms of studied antibiotics the 10-day oral penicillin in powder for oral solution had the lowest cost of course of treatment ($0.59 per 1 kg of a child's body weight). Then clarithromycin ($2.96 per 1 kg), cefuroxime ($4.46 per 1 kg) and azithromycin ($6.74 per 1 kg) were followed in order of cost increasing.

However, considering the differences in clinical effectiveness of studied treatment approaches, direct comparison of the treatment cost does not answer the question of pharmacoeconomic value of antibiotics.

Economic evaluation of short-term course chemotherapy of acute streptococcal pharyngitis in children is presented in the Table 2.

**Economic assessment of short-term course chemotherapy
of acute streptococcal pharyngitis in children**

INN	Brand Names	Cost, USD	Regimen	The cost of treatment per 1 kg, USD	Cost-Effectivness Ratio per 1 kg, USD
Phenoxymethyl penicillin	Penicillin V, powder for oral solution 250 mg/5 mL, 200 mL, TEVA	19.77	10 mg/kg tid for 10 days 13.3 mg/kg tid for 10 days 15 mg/kg tid for 10 days	$0.59 $0.78 $0.88	$21.87 $30.35 $21.94
Clarithromycin	Biaxin, powder for oral suspension 250 mg/5 mL, 50 mL, Abbvie	98.48	7.5 mg/kg bid for 5 days	$2.96	$20.97
Cefuroxime axetil	Ceftin, powder for oral suspension 250 mg/5 mL, 100 mL, GlaxoSmithKline	222.85	10 mg/kg (max 500 mg) bid for 5 days	$4.46	$20.40
Azithromycin	Zithromax, 200 mg/5 mL powder for oral suspension, 30 mL, Pfizer	134.71	20 mg/kg od for 3 days	$6.74	$22.54
Amoxicillin/ clavulanic acid	Augmentin, powder for oral suspension 250 mg/5 mL, 150 mL, GlaxoSmithKline	1260.7	43.8 mg/kg bid (max 1000 mg) for 5 days 40 mg/kg/day for 10 days	$36.81 $67.23	$74.64 -

The **decision-tree model** was constructed for the cost-effectiveness analysis of the acute streptococcal pharyngitis treatment depending on the probability of different outcomes [12].

Cost-effectiveness analysis of the 5-day course of *clarithromycin* and 10-day course of *oral penicillin* is presented on the Figure 1. Calculation results showed that the treatment cost of clarithromycin was in 3.8 times higher than the oral penicillin ($2.96/kg versus $0.78/kg, respectively).

In cases early bacteriological treatment failure and late bacteriological recurrence, patients are prescribed amoxicillin/clavulanate (40 mg/kg/day) per 10 days for $67.23/kg [13].

Considering lower likelihood of early bacteriological treatment failure of clarithromycin (5.6%) compared with oral penicilin (18.1%) and the no significant difference in the likelihood of late bacteriological recurrence after chemotherapy

of clarithromycin and oral penicillin, the financial cost of treating one patient with clarithromycin was:

0.056*($2.96+$67.23)+0.944*0.157*($2.96+$67.23)+0.944*0.843*$2.96=$3.93+ $10.4+$2.36=$16.69 per 1 kg of a child's body weight.

The cost of treating one patient with oral penicillin was:

0.181*($0.78+$67.23)+0.819*0.149*($0.78+$67.23)+0.819*0.851*$0.78=$12.31 +$8.30+$0.54=$21.15 per 1 kg of a child's body weight.

Therefore, the financial cost of short-term therapy with clarithromycin was 26.7% less than the cost of standard therapy with oral penicillin.

The cost-effectiveness ratio (CER) for clarithromycin was equaled $16.69/0.944*0.843=$20.97/kg per treatment success (cure without early bacteriological treatment failure and late bacteriological recurrence); for oral penicillin $21.15/0.819*0.851=$30.35/kg. Thus, the cost per unit of effectiveness of clarithromycin was 44.7% less than the cost per unit of effectiveness of oral penicillin.
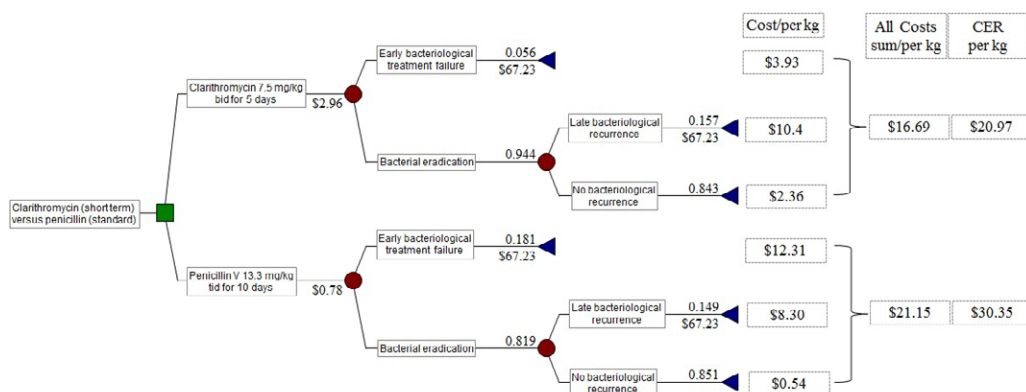

Figure 1. The decision-tree model in pharmacoeconomic analysis of 5-day course of clarithromycin compared with 10-day course of oral penicillin in children with acute streptococcal pharyngitis

The next stage of our research was cost-effectiveness analysis of a 5-day course of oral cefuroxime and 10-day course of oral penicillin. As shown on the Figure 2, the financial costs for treating one patient with cefuroxime and oral penicillin hardly differed ($16.69/kg versus $16.65/kg, respectively). At the same time, the cost per unit of effectiveness of cefuroxime was 7.2% less than the cost per unit of effectiveness of oral penicillin that were equaled $20.40/kg and $22.66/kg, respectively.

The lower cost of the unit of effectiveness of cefuroxime is due to its clinically proven efficacy in the eradication of *Streptococcus pyogenes*. Cefuroxime reduces the probability of a repeated course of antibiotic chemotherapy with amoxicillin/clavulanate.

Seeing the relatively high retail price of cefuroxime, a wide range of its antimicrobial action and insignificant pharmacoeconomic benefits, cefuroxime should be considered as the drug of second-line therapy and used for the treatment of recurrent pharyngitis.
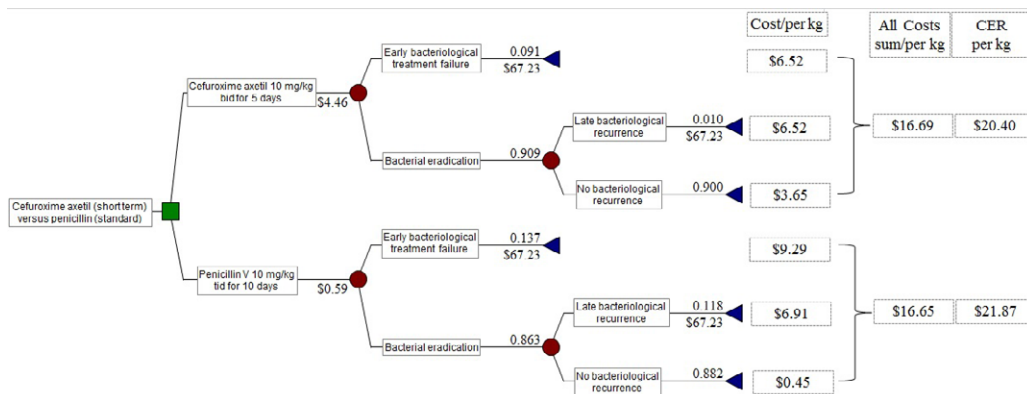
Figure 2. The decision-tree model in pharmacoeconomic analysis of 5-day course of oral cefuroxime compared with 10-day course of oral penicillin in children with acute streptococcal pharyngitis

The cost-effectiveness analysis of a 3-day course of *azithromycin* and 10-day course of *oral penicillin* (Figure 3) showed that the treatment of azithromycin was 10% more expensive than the treatment of oral penicillin ($18.57/kg versus $16.76/kg, respectively). The cost per unit of effectiveness (CER) of azithromycin was $22.54/kg, the CER of oral penicillin - $21.94/kg. Thus, the use of 3-day course of azithromycin is not economically expedient compared with oral penicillin.

Figure 3. The decision-tree model in pharmacoeconomic analysis of 3-day course of azithromycin compared with 10-day course of oral penicillin in children with acute streptococcal pharyngitis

According to expert assessment, which was conducted in our previous study, Ukrainian doctors had considered amoxicillin/clavulanate as the drug of choice for the treatment of acute streptococcal pharyngitis in children [14]. So, on the final stage of our research, we conducted the cost-effectiveness analysis of 5-day course of *amoxicillin/clavulanate* compared with 10-day course of *oral penicillin.*

The Figure 4 shows, that for one unit efficiency of amoxicillin/clavulanate it was necessary to spend 2.6 times more financial resources than for one unit efficiency of oral penicillin. The cost per unit of effectiveness (CER) of amoxicillin/clavulanate was $74.64/kg, the CER of oral penicillin – $29.10/kg.

Moreover, there was no statistically significant clinical benefit in the eradication of *Streptococcus pyogenes* compared with standard therapy oral penicillin (Table. 1). The expenses for 5-day course of amoxicillin/clavulanate were 62.4 times higher than the expenses for 10-day course of oral penicillin ($36.81/kg versus $0.59/kg, respectively).

So, considering the lack of clinical benefits and high cost of treatment, amoxicillin/clavulanate cannot be recommended as first-line drug for the treatment of acute streptococcal pharyngitis in children.
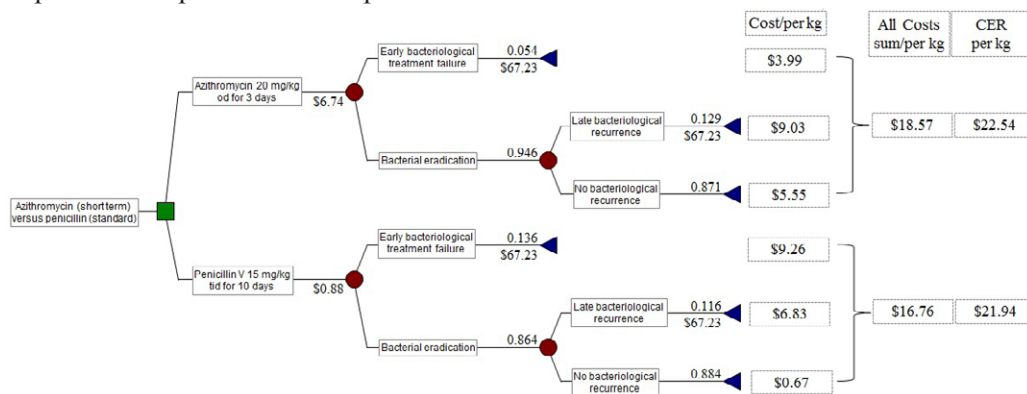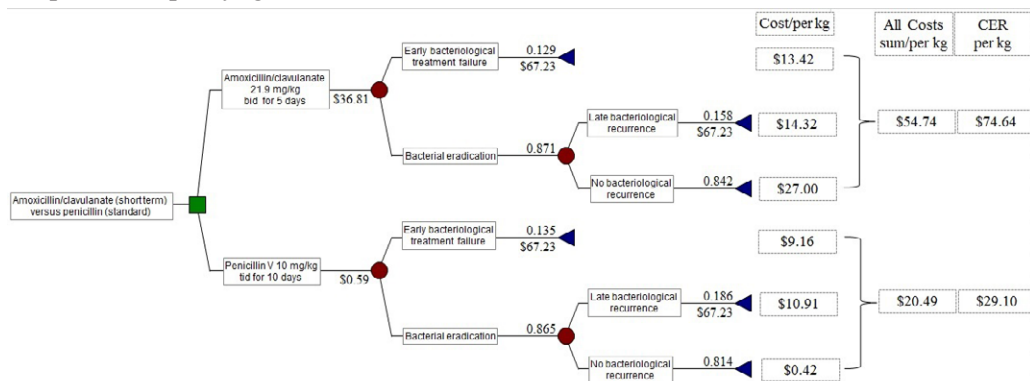

Figure 4. The decision-tree model in pharmacoeconomic analysis of 5-day course of amoxicillin/clavulanate compared with 10-day course of oral penicillin in children with acute streptococcal pharyngitis

In order to determine the stability of the obtained results we conducted sensitivity analysis. Univariant sensitivity analysis of the cost-effectiveness ratio to fluctuations in the retail price of clarithromycin, cefuroxime and amoxicillin/clavulanate within ± 30% confirmed of the results stability. Pharmacoeconomic advantage of oral penicillin over azithromycin lost with 10% reduction in the retail prices.

Conclusions.

1. Direct comparison of the short-term and standard treatment cost showed that the 10-day oral penicillin in powder for oral solution was the lowest among pediatric dosage forms of all studied antibiotics. The cost of treatment was equaled to $0.59 per 1 kg of a child's body weight. The 5-day course of clarithromycin ($ 2.96/kg) was the lowest among the short-term antibiotic courses.

2. Cost-effectiveness evaluation by using the decision-tree model demonstrated the cost-effectiveness ratio (CER) of 5-day course of clarithromycin was 44.7% lower than CER of standard treatment with oral penicillin.

3. The 5-day course of clarithromycin is more expensive for the payer than 10-day course of oral penicillin, but it provides additional efficiency – lesser probability of early bacteriological treatment failure and the need to repeat an antibiotic therapy.

4. The use of 3-day course of azithromycin, 5-day courses of cefuroxime and amoxicillin/clavulanate are pharmacoeconomic inexpedient compared with standard therapy.

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