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THE ECONOMIC BURDEN OF ACUTE BACTERIAL RHINOSINUSITIS AND ACUTE OTITIS MEDIA IN TURKEY: AN EPIDEMIOLOGY BASED COST OF ILLNESS STUDY WITH RESPECT TO CLINICAL PRACTICE AND AVAILABLE GUIDELINES

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ABSTRACT

Objective: To estimate economic burden of acute bacterial rhinosinusitis (ABRS) and acute otitis media (AOM) in Turkey via an epidemiology-based cost of illness study with respect to clinical practice and available guidelines. **Methods:** This cost of illness study was based on identification of per patient direct medical costs and per patient and total annual treatment costs for the management of adult and pediatric patients with ABRS and AOM in Turkey with respect to practice patterns in clinical practice and per guideline recommendations. Average per patient direct medical cost in primary, secondary and tertiary-care management of ABRS and AOM was calculated based on cost items related to physician visits, diagnostic laboratory and radiological tests, drug treatment, hospitalizations and interventions. Total annual treatment cost was calculated via prevalence-based extrapolation of per patient annual treatment costs for different health conditions managed in clinical practice and per guideline recommendations as well as in case of 5% higher antibiotic resistance. **Results:** Average per patient annual treatment costs in clinical practice were US$ 24.29 for pediatric ABRS, US$ 26.83 for adult ABRS, US$ 25.70 for pediatric AOM and US$ 27.10 for adult AOM, while adherence to guidelines was associated with per patient US$ 3.09, US$ 5.84, US$ 2.95 and US$ 2.13 cost reductions, respectively. Total annual treatment cost was US$ 101,499,040 for ABRS and US$ 57,191,330 for AOM in clinical practice along with 20% (US$ 20,260,100) and 9.8% (US$ 5,626,990) cost

reductions, respectively in case of adherence to guidelines. In case of 5% higher antibiotic resistance, total annual antibiotic treatment costs were increased by 18.3% (US$ 18,593,590) in ABRS and by 14.1% (US$ 9,063,630) in AOM. **Conclusions:** In conclusion, our findings indicate that ABRS and AOM pose a considerable burden to health economics in Turkey, with antibiotic prescription identified as the main cost driver and emphasize the likelihood of substantial cost savings by adherence to guideline recommendations and reduced antibiotic resistance.

KEYWORDS: *acute bacterial rhinosinusitis; acute osteomyelitis; practice patterns; cost analysis; antibiotic prescription; clinical practice; guidelines; Turkey.*

INTRODUCTION

Acute rhinosinusitis (ARS) and acute otitis media (AOM) are amongst the health conditions commonly encountered in the primary care practice and associated with high antibiotic prescription rates. In a past study from Turkey, primary care physicians were reported to prescribe antibiotics to all patients with ARS and AOM.[1]

Given that acute rhinosinusitis is usually a self-limiting disease rarely complicated by secondary bacterial infection, antibiotic prescription is considered effective only if a microbiological diagnosis of bacterial etiology or severe disease is evident.[2,3] However, uncertainty in targeting patients who need antibiotic therapy due to difficulty in differential diagnosis of bacterial or viral origin as well as patients' demand on initiating antibiotics leads to an overprescribing of antibiotics in up to 85% of visits, and thus potential risk of antibacterial resistance.[4,5] Poor adherence to guideline recommendations on prescribing antibiotics in ABRS by physicians has also been associated with frequent prescription of more expensive yet less effective medications and thus the risk of bacterial resistance and increased cost.[6]

Acute otitis media (AOM) is also a very common respiratory tract infection more commonly reported in children and affecting millions of young children worldwide each year. AOM is considered to be a leading cause of physician visits that accounts for a considerable percentage of all outpatient antibiotic prescriptions and a major contributor to healthcare costs.[7-9]

AOM and ABRS share similar pathogenicity with Streptococcus pneumoniae (*S. pneumoniae*), Haemophilus influenzae (*H. influenza*) and Moraxella catarrhalis (*M. catarrhalis*) as the predominant organisms.[9-12] From an economic perspective, since ABRS and AOM are frequent diseases with similar pathogenesis but no precise diagnostic criteria, while associated with frequent physician visits, increased healthcare utilization rates, extensive antibiotic prescription and growing antibiotic resistance,[10] it is important to have country-specific epidemiological data on the incidence and cost of illness of ABRS and AOM episodes for policy makers for informed planning of health care budgets and research investments and for formulating cost-effectiveness analyses.[13]

This cost of illness study was therefore designed to determine per patient direct medical costs and per patient and total annual treatment costs for the management of adult and pediatric patients with ABRS and AOM in Turkey with respect to practice patterns applied in clinical practice and recommended by guidelines.

METHODS

Design

This cost of illness study was based on identification of per patient direct medical costs and per patient and total annual treatment costs for the management of adult and pediatric patients with ABRS and AOM in Turkey with respect to practice patterns in clinical practice and per guideline recommendations. Average per patient direct medical cost in first-line, second-line and third-line management of ABRS and AOM was calculated based on cost items related to physician visits, diagnostic laboratory and radiological tests, drug treatment, hospitalizations and interventions. Total annual treatment cost was calculated via prevalence-based extrapolation of per patient annual treatment costs for different health conditions managed in clinical practice and per guideline recommendations as well as in case of 5% higher antibiotic resistance.

Epidemiological data on real life clinical practice

Literature review of epidemiological studies published to date in Turkey on the management of pediatric (aged 0-15 years) and adult (>15 years) patients with ABRS and AOM was performed to identify practice patterns in real-life clinical practice including outpatient clinic admission rates, diagnostic laboratory and radiological work-up, selected antibiotic regimens, treatment related adverse event rates, hospitalizations and interventions as well as disease prevalence and current status of antibiotic resistance in ABRS and AOM.

Reference guidelines

Guidelines provide a basis for the cost analysis included European Position Paper on Rhinosinusitis and Nasal Polyps Group (EPOS) 2007 Guidelines on the Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps,[14] EPOS 2012 European position paper on rhinosinusitis and nasal polyps,[15] Infectious Diseases Society of America (IDSA) 2012 clinical practice guideline for acute bacterial rhinosinusitis in children and adults,[16] American Academy of Pediatrics (AAP) 2001 clinical practice guideline on management of sinusitis,[17] AAP 2013 Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years,[18] Canadian 2011 clinical practice guidelines for acute and chronic rhinosinusitis,[19] American Academy of Otolaryngology-Head and Neck Surgery Foundation updated clinical practice guideline for adult sinusitis,[20] AAP-American Academy of Family Physicians (AFAP) 2004 release guideline on diagnosis and management of acute otitis media,[21] and American Academy of Pediatrics 2004,[22] and 2013,[23] Guidelines for the diagnosis and management of acute otitis media and local guidelines.[24,25]

Cost analysis

Average per patient direct medical costs were calculated based on cost items including physician visits, diagnostic laboratory and radiological tests, drug treatment, hospitalizations and interventions from payer perspective (only direct medical costs using prices of the public payer "Social Security Institution (SSI)" in Turkey), using cost of illness method developed by WHO.[26] For drugs, retail prices from the updated price list and updated institution discount list of SSI for August 2016 were taken into account in calculation of the unit costs.[27] Costs related to diagnostic tests were calculated considering the Health Implementation Notification by SSI.[28] Physician visits costs were calculated using unit prices also based on the same SSI notification.[28] Hospitalization costs were calculated using unit prices based on Healthcare Organization Price List in Health Practice Declaration and Treatment Assist Practice Declaration. Monetary results were converted by using 2.97 USD/TL September 2016 exchange rate. Direct non-medical costs of different origin (e.g. transfers of patient and caregivers for examinations and/or hospitalization, home care, etc.) and indirect costs were not included in the cost analysis.

Per patient annual treatment costs were also calculated via a treatment tree model software (Treeage Pro 2015, healthcare version v15.2.2.0; Treeage® Software Inc, USA) by entering

average cost of each treatment strategy based on probability of specific health conditions/outcomes associated with the selected treatment strategy in clinical practice or per guideline recommendations into the model (Fig 1). The model begins with a initial node with a branch for each treatment option (treatment with or without antibiotic prescription, immediate or delayed antibiotic prescription, treatment related adverse events necessitating or not necessitating treatment switch and antibiotic resistance) and a subtree for each treatment option that follows the condition through treatment, including any number of possible outcomes. Per patient annual treatment costs provided by the model for treatments applied in clinical practice and appropriate per guideline recommendations were extrapolated using national disease-specific prevalence data to determine total annual treatment costs. Total costs related to treatment of ABRS and AOM was evaluated with respect to prescription strategies used in real-life clinical practice versus per guideline recommendations as well as in case of 5% higher antibiotic resistance rates.

Unit costs

Unit costs for physician visits item were calculated based on data on primary, secondary and tertiary care outpatient clinic admission rates for ABRS (31.7%, 62.8% and 5.5%, respectively) and AOM (20.4%, 77.6% and 2.0%, respectively) in Turkey as well as Health Implementation Notification by SSI (24,28,29) (Table 1).

Unit costs for drug treatments used per an ABRS or AOM episode were calculated based on treatment algorithms recommended by APA guidelines for ARBS (16,30,31) and AOM.[23] in accordance with age-weighted.[32-34] reference body weight values available for Turkish children.[35] and 10-14 days of treatment duration in both pediatric and adult patients (Table 1).

Unit costs for treatment related adverse events were calculated by weighing adverse events and related treatment switch or discontinuation rates reported in epidemiological studies in Turkish ABRS and AOM patients,[36-53] with respect to prescribed antibiotic regimens. Macrolides (28.6%), second generation cephalosporins (26.5%) and amoxicillin/clavulanate (20.4%) were the most common antibiotics prescribed in pediatric ABRS, amoxicillin/clavulanate (43.3%), second generation cephalosporins (21.6%) and third generation cephalosporins (16.2%) in pediatric AOM, amoxicillin/clavulanate (31.1%), quinolones (19.1%) and second generation cephalosporins (16.5%) in adult ABRS and amoxicillin/clavulanate (50.2%) and second generation cephalosporins (29.4%) in adult

AOM. Accordingly, adverse event and treatment discontinuation rates used in estimation of unit costs were 15.4% and 2.4% in pediatric ABRS, %23.7 and %1.9 in adult ABRS, 18.3% and 1.7% in pediatric AOM, and 17.1% and %2.0 in adult AOM, respectively,[36-53] (Table 2).

Antibiotic resistance rates

Antibiotic resistance rates were determined based on national data on antibiotic resistance rates reported for *S. pneumoniae* (62% for penicillin, 49% for erythromycin,35.4% for cefuroxime, 24% for ceftriaxone, 5% for amoxicillin/clavulanate and levofloxacin), *H. influenzae* (100% for penicillin, 6% for cefaclor, 5% for amoxicillin/clavulanate, 4% for levofloxacin and 3% for cefuroxime), *M. catarrhalis* (100% for penicillin, 5.6% for erythromycin and 7.4% for cefuroxime).[54-56]

Diagnostic and practice patterns

Distribution of diagnostic and practice patterns in the primary care, secondary care and tertiary care management of pediatric and adult patients with ABRS and AOM are presented in Table 3 with respect to data from clinical practice,[24,29,57-62] and associated guideline or expert consensus recommendations.[14-24,57,60-64]

Probability of health conditions included in the Treeage Pro model

Probability of each health condition in clinical practice or in guideline based management of pediatric and adult patients with ABRS and AOM was also determined (Table 4) and provided basis for calculation of per patient annual treatment costs in the model.

Statistical analysis

Descriptive statistics were used to summarize results on practice patterns for the ABRS and AOM management. Expenses related to diagnosis, treatment and follow-up of ABRS and AOM were the main cost-analysis related parameter of the study. Cost model was based on the following equation: "Cost = ∑ (Frequency; %) X (Unit price; US$) X (patient ratio; %)".

RESULTS

Average per patient direct medical cost for ABRS and AOM management

Average per patient direct medical cost for the first/second/third line management were US$ 16.75/ US$ 36.72/ US$ 406.00 in clinical practice and US$ 18.71/ US$ 38.68/ US$ 408.05 per guideline recommendations in pediatric ABRS, while US$ 20.88/ US$ 39.46/ US$ 386.77

in clinical practice and US$ 18.72/ US$ 37.34/ US$ 384.28 per guideline recommendations in adult ABRS (Table 5).

Average per patient direct medical cost for the first/second/third line management were US$ 22.29/ US$ 34.11/ US$ 317.31 in clinical practice and US$ 20.71/ US$ 32.53/ US$ 315.70 per guideline recommendations in pediatric AOM, while US$ 21.55/ US$ 57.41/ US$ 237.68 in clinical practice and US$ 20.27/ US$ 56, 13/ US$ 236.40 per guideline recommendations in adult AOM (Table 5).

Treatment tree model output for per patient annual treatment costs

Run of model with input data on direct costs (Table 5) and probabilities (Table 4) of each health condition revealed output data on clinical practice and guideline based per patient annual treatment costs to be US$ 24.29 and US$ 21.20 (per patient US$ 3.09 cost reduction with adherence to guidelines), respectively in pediatric ABRS, while to be US$ 26.83 and US$ 20.99 (per patient US$ 5.84 cost reduction with adherence to guidelines), respectively in adult ABRS (Table 6).

Clinical practice and guideline based per patient annual treatment costs were US$ 25.70 and US$ 22.75 (per patient US$ 2.95 cost reduction with adherence to guidelines), respectively in pediatric AOM, while US$ 27.10 and US$ 24.97 (per patient US$ 2.13 cost reduction with adherence to guidelines), respectively for adult AOM (Table 6).

Total annual antibiotic treatment costs

Prevalence of ABRS in Turkey was reported to be 20.3% (57), while 2005 data from Ministry of Health statistics revealed total 1,905,136 cases (21.6% pediatric, 78.4% adult) were diagnosed with ABRS in primary care admissions.[65] Accordingly, the number of patients with ABRS in Turkey in 2015 was estimated to be 3,862,016 including 834,195 pediatric patients and 3,027, 821 adult patients (Table 7).

Extrapolation of per patient antibiotic treatment costs to the overall ABRS patient population revealed that total annual ABRS treatment cost was US$ 101,499,040.0 in clinical practice and US$ 81,238,890.0 according to guideline recommendations with 20% (US$ 20,260,100) cost reduction in case of adherence to guidelines (Table 7).

Prevalence and incidence of AOM in Turkey were reported to be 9.2% (56.0% pediatric, 44.0% adult) and 0.46, respectively,[71, 80] Accordingly, the number of patients with ABRS in

Turkey in 2015 was estimated to be 2,173,253 including 1,217,021 pediatric patients and 956,232 adult patients (Table 7).

Extrapolation of per patient antibiotic treatment costs to the overall patient population revealed that total annual AOM treatment cost was US$ 57,191,330.0 in clinical practice and US$ 51,564,340.0 according to guideline recommendations with 9.8% (US$ 5,626,990.0) cost reduction in case of adherence to guidelines (Table 7).

The impact of antibiotic resistance on total treatment costs

Calculation of treatment costs with use of 5% higher antibiotic resistance rates as an input in the model revealed per patient annual antibiotic treatment cost to be US$ 30.50 for pediatric and US$ 31.26 for adult patients with ABRS, while to be US$ 29.54 for pediatric and US$ 30.76 for adult patients with AOM (Table 8).

Extrapolation of per patient treatment costs associated with 5% higher antibiotic resistance to the overall patient population revealed that 5% increase in antibiotic resistance increased total annual antibiotic treatment costs by 18.3% (US$ 18,593,590.0; from US$ 101,499,040.0 to US$ 120,092,630.0) in ABRS and by 14.1% (US$ 8,063,630.0; from US$ 57,191,330.0 to US$ 65,254,960.0) in AOM (Table 8).

DISCUSSION

Cost analysis

Our findings revealed significant economic burden of managing ABRS and AOM in clinical practice with considerable per patient direct medical cost estimated for pediatric ABRS (US$ 16.75 in first line, US$ 406.00 in second line), adult ABRS (US$ 20.88 in first line, US$ 386.77 in third line), pediatric AOM (US$ 22.29 in first line, US$ 317.31 in third line) and adult AOM (US$ 21.55 in first line, US$ 237.68 in third line).

Estimated total costs per episode of AOM in past studies was reported to range from US$108 to US$1,330 in USA excluding indirect costs,[8,66] to range from US$ 16.1 (in Oman) to US$ 33.6 (in Turkey) and US$ 67.1 (in Saudi Arabia) in Middle Eastern countries,[13] to be US$ 28 (not including complications and hospitalizations) in Turkey.[67]

Mean total cost of rhinosinusitis care was reported to be US$ 147.6 per success, US$ 242.9 per failure and US$ 205.5 per relapse in a retrospective database study of 2633 rhinosinusitis episodes identified from the records of 34,348 asthma patients in USA in 1997.[68] Estimated

direct medical costs for symptomatic treatment, clinical criteria-based treatment, empirical treatment and radiographic-guided treatment of ABRS were reported to be US$ 20; US$ 24.50, US$ 35 and US$ 105.50 per patient, respectively in a meta-analysis of data from the USA Agency for Health Care Policy and Research evidence-based report.[10]

The estimated annual cost of AOM episodes was reported to be US$ 3 to US$ 5 billion in USA,[8,66,69,70] US$ 3.3 million (in children aged <20 years) in New Zealand in 2006–2007,[71] US$138 million in Finland,[72] US$ 611.0 million (US$ 140.3 million for indirect cost, US$ 428.4 million for children aged ≤14 years) in Canada in 1994,[73] US $1.8 billion (children below 4 years of age) in Japan,[74] US$ 166.1 to US$ 407.7 million (children aged< 5 years) in 2008 in Australia,[75] and US$ 61,152,000 in Turkey.[67]

Although international comparisons of the economic cost are subject to difficulties necessitating adjustments for differences in the financing and delivery of services as well as impacts of disease on indirect costs due to varied labor market and caregiving practices,[72,76,77] our results confirm that ABRS and AOM causes a substantial burden to public health, emphasizing the need for cost-effective prevention strategies.[3,12,13,73]

Besides, indirect costs were not included and thus true impact of AOM and ABRS on healthcare economics in Turkey seems likely to be underestimated in our analysis since both diseases also generate a substantial social burden and an indirect cost.[7,8,78,79]

In our analysis of per patient direct medical costs, antibiotic treatment was identified as the main cost driver in the clinical practice or guideline-based first-line, second-line and third-line treatment of pediatric and adult patients with ABRS and adult patients with AOM. In pediatric patients with AOM, antibiotic treatment was the main cost driver in the first-line and second-line treatment, whereas hospitalizations and interventions was the main cost driver in the third-line treatment.

Legends to the Figures

Fig 1. Treeage Pro treatment model used for per patient annual treatment cost related to management of pediatric/adult acute bacterial rhinosinusitis and acute osteomyelitis in clinical practice and per guideline recommendations.

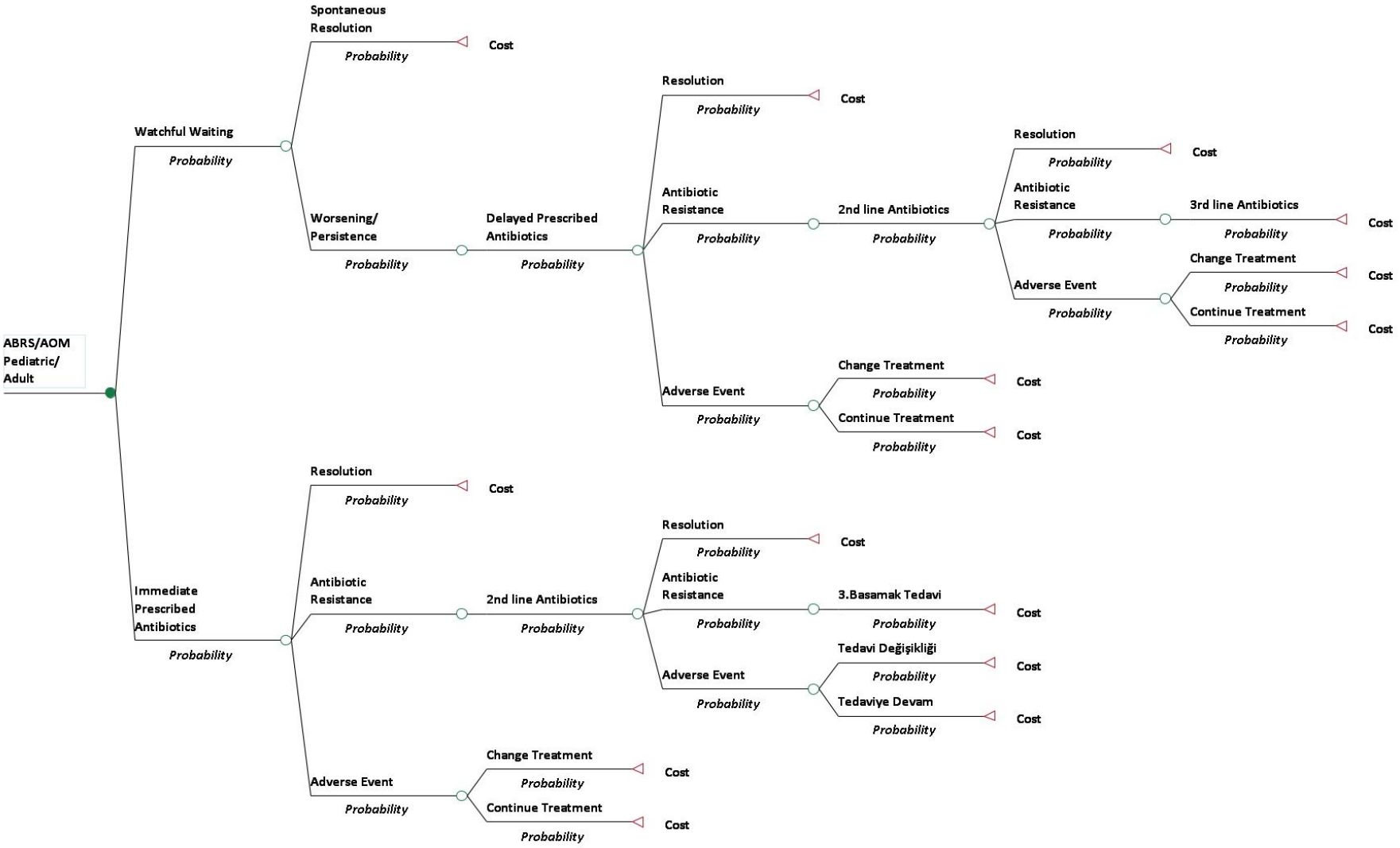
ABRS/AOM
Pediatric/
Adult
Watchful Waiting
Probability
Spontaneous
Resolution
Probability
Cost
Worsening/
Persistence
Probability
Delayed Prescribed
Antibiotics
Probability
Resolution
Probability
Cost
Antibiotic
Resistance
Probability
2nd line Antibiotics
Probability
Resolution
Probability
Cost
Antibiotic
Resistance
Probability
3rd line Antibiotics
Probability
Cost
Adverse Event
Probability
Change Treatment
Probability
Cost
Continue Treatment
Probability
Cost
Adverse Event
Probability
Change Treatment
Probability
Cost
Continue Treatment
Probability
Cost
Immediate
Prescribed
Antibiotics
Probability
Resolution
Probability
Cost
Antibiotic
Resistance
Probability
2nd line Antibiotics
Probability
Resolution
Probability
Cost
Antibiotic
Resistance
Probability
3.Basamak Tedavi
Probability
Cost
Adverse Event
Probability
Tedavi Değişikliği
Probability
Cost
Tedaviye Devam
Probability
Cost
Adverse Event
Probability
Change Treatment
Probability
Cost
Continue Treatment
Probability
Cost

Fig. 1:

Table 1: Unit costs for outpatient admissions and drug treatments.[24,28,29,31]

		Unit cost for outpatient admission (US$)			
		ABRS		AOM	
Outpatient clinics					
Family medicine –primary care		3.20		3.20	
Family medicine –secondary care		8.59		8.59	
Pediatrics		9.49		9.16	
Ear Nose and Throat		8.79		8.45	
Internal Medicine		10.64		10.13	
Infectious Diseases		10.34		9.87	
Chest Diseases		10.00		9.60	
		Unit cost for drug treatment per episode (US$)[a]			
		Pediatric		Adult	
		ABRS	AOM	ABRS	AOM
Drug regimens					
Amoxicillin			5.22		15.8
Amoxicillin/ clavulanate	Total	8.35	8.35	27.0	22.0
	For high dose	14.88		47.1	
	For a ratio of 14:1		7.85		
2nd generation cephalosporins		5.93	5.93	8.18	7.61
Macrolides		2.83	2.83	7.34	7.34
3rd generation cephalosporins		12.76	12.76	18.22	12.53
Ceftriaxone	3-day treatment		9.97		35.52
	PE included	114.51		172.29	
Cefotaxime (PE included)		237.91		308.75	
Ampicillin/ sulbactam	Oral	10.24	10.24	10.57	7.10
	PE	179.39		231.99	
Beta-lactam		4.38	4.38	7.98	5.32
1st generation cephalosporins		23.10		29.09	
Clindamycin		29.33	29.33		31.08
Fluoroquinolones				13.80	12.96
Levofloxacin	Oral			11.89	
	PE			145.93	
Moxifloxacin				12.36	
Doxycycline				3.91	
Trimethoprim/sulfamethoxazole				4.75	2.93
Aminoglycosides			9.02		8.08
Analgesic/antipyretics		5.35	5.35	3.94	4.48
Decongestants			1.45		1.65

ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media
[a]calculated based on age group and body weight in pediatric patients and for 10-14 days of treatment for pediatric and adult patients

Table 2: Rates for antibiotic prescription, adverse events and related outcomes.[36-53]

	ABRS			AOM		
	Prescription rate	**Adverse event**	**Treatment switch**	**Prescription rate**	**Adverse event**	**Treatment discontinuation**
Pediatric patients	%	%	%	%	%	%
Amoxicillin/clavulanate	20.4	4.5	0.1	43.3	9.5	0.2
2nd generation cephalosporins	26.5	4.0	1.4	21.6	3.3	1.1
Macrolides	28.6	3.0	0.6	5.4	0.6	0.1
3rd generation cephalosporins	12.3	3.5	0.0	16.2	4.6	0.0
Ampicillin/sulbactam	6.1	0.3	0.2	2.7	0.1	0.1
Beta-lactam	4.1	0.1	0.1	5.4	0.2	0.2
1st generation cephalosporins	2.0	0.0	0.0	-	-	-
Aminoglycosides	-	-	-	5.4	0.0	0.0
Total	100.0	15.4	2.4	100.0	18.3	1.7
Adult patients	%	%	%	%	%	%
Amoxicillin/clavulanate	31.1	4.9	0.9	50.2	8.0	1.5
Quinolones	19.1	7.3	0.2	5.0	1.9	0.1
2nd generation cephalosporins	16.5	1.2	0.0	29.4	2.1	0.0
Macrolides	12.0	3.7	0.3	4.1	1.2	0.1
3rd generation cephalosporins	9.8	3.6	0.3	2.7	1.0	0.1
TMP-SMX	2.8	0.0	0.0	1.3	0.0	0.0
Ampicillin/sulbactam	2.4	1.1	0.1	1.8	0.8	0.1
Beta-lactam	4.1	1.9	0.1	4.5	2.1	0.1
1st generation cephalosporins	2.2	0.0	0.0	-	-	-
Aminoglycosides	-	-	-	1.0	0.0	0.0
Total	100.0	23.7	1.9	100.0	17.1	2.0

Table 3: Diagnostic and practice patterns in clinical practice and per guideline recommendations.[14-25,29,32-34,57-64]

	ABRS				AOM			
	Clinical practice		Guidelines		Clinical practice		Guidelines	
	Pediatric	**Adult**	**Pediatric**	**Adult**	**Pediatric**	**Adult**	**Pediatric**	**Adult**
First Line								
Outpatient admission, %								
Family Health Center	21.4	21.4	21.4	21.4	14.1	13.8	14.1	13.8
Family Medicine	46.2	46.2	46.2	46.2	53.5	52.5	53.5	52.5
Pediatrics	21.2		21.2		21.2		21.2	
Ear Nose and Throat	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2
Internal Medicine		19.0		19.0		20.3		20.3
Infectious Diseases		1.1		1.1		1.1		1.1
Chest Diseases		1.1		1.1		1.1		1.1

First admission, %								
Diagnostic tests	2.9	2.9		2.9	2.9	2.9	2.9	2.9
Hospitalization or intervention	0	0		0	0	0	0	0
Antibiotic prescription	94.5	94.5		94.5	90.9	90.9	90.9	90.9
Amoxicillin/clavulanate	20.4	31.1	98.0	92.0	43.3	50.2	49.0	46.0
2nd generation cephalosporins	26.6	16.5			21.6	29.4	2.0a	8.0a
Macrolides	28.6	11.9			5.4	4.1		
3rd generation cephalosporins	12.2	9.8	2.0b		16.2	2.7		
Ampicillin/sulbactam	6.1	2.4			2.7	1.8		
Beta-lactam	4.1	4.1			5.4	4.5		
1st generation cephalosporins	2.0	2.2						
Quinolones	-	19.1				5.0		
TMP-SMX		2.9				1.4		
Tetracycline				8.0c				
Aminoglycosides					5.4	0.9		
Amoxicillin							49.0	46.0
Analgesic/antipyretics	40.8	55.4	40.8	55.4	89.4	89.4	89.4	89.4
Decongestants					100.0	100.0	100.0	100.0
Second Line	Admission distributed equally amongst clinics (21.4% for each) Diagnostic tests included in the admission cost High dose amoxicillin/clavulanate in pediatric patients, high dose amoxicillin/clavulanate (50%) or quinolones (50%) in adults				Admission distributed equally amongst clinics in pediatric patients (14.1% for each), admission to ENT clinics in adults (100%) Pediatric and adult patients receive amoxicillin/clavulanate (50%) or ceftriaxone (50%)			
Third Line	Admission equally to Pediatrics and ENT clinics (3.6% for each) Sinus CT/MRI (50% for each); hospitalization for i.v. interventions PE ampicillin/sulbactam, ceftriaxone or cefotaxime (33% for each) in pediatric patients; PE ampicillin/sulbactam, ceftriaxone, cefotaxime or levofloxacin; oral levofloxacin or moxifloxacin (16.6% for each) in adults				ENT clinics (100%); hospitalization for i.v. interventions Tympanometry (100%), tube placement/ear MR (13.5%) in pediatric patients Ear MRI(100%) in adult patients Parenteral ceftriaxone + clindamycin in pediatric and adult patients			

ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media, ENT: and Ear Nose and Throat, PE: parenteral, TMP-SMX: Trimethoprim/sulfamethoxazole [a]in patients with penicillin allergy [b]plus clindamycin, [c]doxycycline

Table 4: Probability of health conditions included in the Treeage Pro model.

Health conditions	Probability (%)							
	ABRS				AOM			
	Pediatric		Adult		Pediatric		Adult	
	Clinical practice	Guidelines	Clinical practice	Guidelines	Clinical practice	Guidelines	Clinical practice	Guidelines
First line management								
Treatment without antibiotic prescription	5.5	5.5	5.5	5.5	9.1	9.1	9.1	9.1
Delayed antibiotic prescription	31.0	31.0	45.0	45.0	31.0	31.0	45.0	45.0
Adverse event in delayed antibiotic prescription	6.5	9.3	9.9	7.4	8.0	5.5	7.2	12.0
Adverse event and treatment switch in delayed antibiotic prescription	15.4	1.8	19.7	37.8	21.3	36.3	27.8	24.0
Immediate antibiotic prescription	94.5	94.5	94.5	94.5	90.9	90.9	90.9	90.9
Adverse event	15.4	22.1	23.7	17.7	18.3	13.2	17.1	28.5
Adverse event necessitating treatment switch	37.0	8.8	8.0	15.8	9.0	15.0	11.7	10.0
Failure of treatment due to antibiotic resistance	19.1	5.0	12.2	5.0	13.8	8.8	12.5	8.8
Second line management								
Adverse event	22.0	22.1	27.1	27.1	13.9	13.9	10.0	10.0
Adverse event necessitating treatment switch	8.8	8.8	7.7	7.7	2.0	2.0	3.5	3.5
Failure of treatment due to antibiotic resistance	5.0	5.0	3.3	3.3	5.0	5.0	5.0	5.0
Adverse event	9.3	9.3	11.4	11.4	6.0	6.0	4.2	4.2

in delayed antibiotic prescription								
Adverse event and treatment switch in delayed antibiotic prescription	1.8	1.8	18.4	18.4	11.9	11.9	84.0	84.0
ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media								

Table 5: Per patient direct medical cost of first, second and third line management in ABRS and AOM in clinical practice and per guideline recommendations.

		Per patient direct medical cost (US$)											
		Pediatric						Adult					
		Clinical practice			Guideline recommendations			Clinical practice			Guideline recommendations		
		First line	Second line	Third line	First line	Second line	Third line	First line	Second line	Third line	First line	Second line	Third line
ABRS													
Cost items	Physician visit	7.64	9.56	10.87	7.64	9.56	10.87	7.88	9.90	11.28	7.88	9.90	11.28
	Laboratory tests	0.00	0.00	50.73	0.00	0.00	50.73	0.00	0.00	50.74	0.00	0.00	50.74
	Hospitalization	0.00	0.00	134.67	0.00	0.00	134.67	0.00	0.00	134.68	0.00	0.00	134.68
	Interventions	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Drug treatment	9.11	27.16	209.82	11.07	29.12	211.78	13.00	29.56	190.07	10.84	27.44	187.58
	Total	16.75	36.72	406.00	18.71	38.68	408.05	20.88	39.46	386.77	18.72	37.34	384.28
AOM													
Cost items	Physician visit	7.95	9.16	25.56	7.95	9.16	25.53	8.18	15.59	24.01	8.18	15.59	24.01
	Laboratory tests	0.00	1.11	41.89	0.00	1.11	41.89	0.00	6.53	52.90	0.00	6.53	52.90
	Hospitalization	0.00	0.00	40.40	0.00	0.00	40.40	0.00	0.00	40.40	0.00	0.00	40.40
	Interventions	0.00	0.00	140.98	.00	0.00	140.98	0.00	0.00	14.01	0.00	0.00	14.01
	Drug treatment	14.34	23.84	68.48	12.76	22.26	66.90	13.37	35.29	106.36	12.09	34.01	105.08
	Total	22.29	34.11	317.31	20.71	32.53	315.70	21.55	57.41	237.68	20.27	56.13	236.40
ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media													

Table 6: Treeage Pro Model output for per patient treatment costs.

	Per patient treatment cost (US$)		
	Clinical practice	**Guidelines**	**Cost difference**
ABRS			
Pediatric	24.29	21.20	3.09
Adult	26.83	20.99	5.84
AOM	.	.	.
Pediatric	25.70	22.75	2.95
Adult	27.10	24.97	2.13
ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media			

Table 7: Per patient and total annual treatment costs with respect to clinical practice and guideline recommendations.

		Per patient annual cost (1,000US$)		**Total annual cost (1,000US$)**	
		Clinical practice	**Guidelines**	**Clinical practice**	**Guidelines**
ABRS					
# of pediatric patients	834,195	24.29	21,20	20,262.60	17,684.93
# of adult patients	3,027,821	26.83	20,99	81,236.44	63,553.96
Total patient number	3,862,016			101,499.04	81,238.89
			Difference (1,000US$)	**20,260.1**	
			%	**20**	
		Per patient annual cost (US$)		**Total annual cost (US$)**	
		Clinical practice	Guidelines	Clinical practice	Guidelines
AOM					
# of pediatric patients	1,217,021	25.70	22.75	31,277.44	27,687.23
# of adult patients	956,232	27.10	24.97	25,913.89	23,877.11
Total patient number	2,173,253			57,191.33	51,564.34
			Difference (1,000US$)	**5,626.99**	
			%	**9.8**	

ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media

Table 8: Per patient and total annual treatment costs with respect to antibiotic resistance.

		Per patient annual cost (US$)		Total annual cost (US$)	
		Treatment	**5% increase in antibiotic resistance**	**Treatment**	**5% increase in antibiotic resistance**
ABRS					
# of pediatric patients	834,195	24.29	30.50	20,262.60	25,442.95
# of adult patients	3,027,821	26.83	31.26	81,236.44	94,649.68
Total patient number	3,862,016			101,499.04	120,092.63
			Difference (1,000US$)	**18,593,59**	
			%	**18.3**	
		Per patient annual cost (US$)		**Total annual cost (US$)**	
		Treatment	5% increase in antibiotic resistance	Treatment	5% increase in antibiotic resistance
AOM					
# of pediatric patients	1,217,021	25.70	29.45	31,277.44	35,841.27
# of adult patients	956,232	27.10	30.76	25,913.89	29,413.69
Total patient number	2,173,253			57,191.33	65,254.96
			Difference (1,000US$)	**8063.63**	
			%	**14.1**	
ABRS: Acute bacterial rhinosinusitis, AOM: Acute otitis media					

Decision tree model based cost analysis revealed per patient annual antibiotic prescription costs in clinical practice to be US$ 24.29, US$ 26.83, US$ 25.70 and US$ 27.10 in pediatric ABRS, adult ABRS, pediatric AOM and adult AOM, respectively. This seems consistent with total antibiotic expenditures per episodes of AOM reported to range from US$ 165 to US$ 244,[80] and estimates for clinical criteria-based treatment (US$ 24.50) and empirical treatment (US$ 35) in acute rhinosinusitis.[10]

Extrapolation of per patient treatment costs to the overall ABRS and AOM patient population in Turkey in the present study revealed that total annual antibiotic prescription cost was US$

101,499,040 in ABRS and US$ 57,191,330 in AOM in clinical practice. This emphasizes the financial implications of strategies used to target patients who need antibiotic therapy as well as choice of the initiating antibiotic in an ABRS or AOM episode.[3,80]

In fact, use of delayed strategies in upper respiratory tract infections when there is reasonable uncertainty rather than a supposedly bacterial infection or critical illness have been associated with significant advantages over immediate antibiotic prescription in terms of reducing antibiotic consumption.[81-83]

Antibiotic regimens and antibiotic resistance

Substantial change in epidemiology of causative organisms over the years, particularly with the emergence of resistance in *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*,[3] resulted in use of more recent and more expensive antibacterial agents with a broader spectrum of antibacterial activity (e.g. amoxicillin plus a β-lactamase inhibitor, or a fluoroquinolone active against Gram-positive organisms or one of the newer generation cephalosporins.[3,11,84] Hence, prescription of amoxicillin-clavulanate instead of amoxicillin as followed by cephalosporins as the first-choice antibiotic in pediatric and adult AOM population and followed by quinolones and cephalosporins in adult ABRS population in Turkey seems consistent with current status of antibiotic resistance for *S pneumoniae, H influenza* and *M catarrhalis* in our country.[54-56] Given the cost-effectiveness of amoxicillin prescription as compared with other antibiotic regimens.[85] selection of regimens compatible for current antibiotic resistance status in Turkey seems to translate into the identification of antibiotic prescription costs as the main cost driver in our analysis.

Antibiotic resistance has a considerable impact on health care expenditure, medical outcomes and measures to control infectious disease.[86,87] Patients infected with resistant strains as compared with drug-susceptible strains of bacteria are considered to be more expensive to treat due to cost increments associated with use of new and more expensive antibiotics including fluoroquinolones, oral cephalosporins, and macrolides.[86,88,89]

Notably, extrapolation of per patient treatment costs in case of 5% higher antibiotic resistance to the overall patient population revealed total annual treatment cost for ABRS to increase from US$ 101,499,040 to US$ 120,092,630 with 18.3% (US$ 18,593,590) cost increment and total annual treatment costs for AOM to increase from US$ 57,191,330 to US$ 65,254,960 with 14.1% (US$ 8,063,630) cost increment in our analysis.

Adherence to guidelines

Clinical judgment and local resistance patterns are considered paramount in selecting antibiotics along with adherence to guideline recommendations updated in terms of local antimicrobial resistance status.[16,90,91] Accordingly, besides prevention of irrational use of antibiotics (i.e. use of antibiotics for viral infections, unnecessarily prescribing broad-spectrums, use of inappropriate doses and durations and patients' self-treatments), the potential role of greater use of delayed prescription, through decreased antibiotic use, has also been emphasized in reducing the rates of antibiotic resistance and the associated health expenditures.[2,61,92-96]

Physicians are considered to have a key role in the achievement of initiatives and regulations relevant to irrational use of antibiotics consistent with their primary responsibility in prescribing practices.[61,97,98]

In this regard, it should be noted that adherence rates to AOM and ABRS guidelines from several countries published in recent years indicate an overall low-to-moderate compliance rates among physicians and thus the potential risk of antibiotic overprescribing as varied between countries depending on national recommendations, health care systems, practice patterns, patient expectations and impact of marketing by pharmacies and pharmaceutical companies.[5,67,99-104]

In a web-based cross-sectional survey of physicians from Turkey, while 31% of physicians identified that "viruses" as the main pathogens of AOM, 62% of them reported still to prescribe antibiotics.[67] Similarly, in an Italian study while the majority of physicians stated observation for selected AOM cases to be a reasonable option, only 10% reported to treat with observation.[102]

Accordingly, in our study, decision tree model based cost analysis of antibiotic treatment considering different treatment scenarios revealed that adherence to guidelines was associated with US$ 3.09 (pediatric ABRS) and US$ 5.84 (adult ABRS), US$ 2.95 (pediatric AOM) and US$ 2.13 (adult AOM) cost reduction in per patient annual antibiotic treatment costs as compared with costs in clinical practice which refers overall US$ 20,260,100 (20%) and US$ 5,626,990 (9.8%) cost savings in total annual antibiotic prescription cost in ABRS and AOM, respectively. Notably, cost savings associated with adherence to guidelines in treating ABRS

and AOM refer to 4.8% and 1.3% of total antibiotic treatment budget spent by SSI per year in our country, respectively.

Similarly, in an analysis of 2006-2010 US national database for antibiotic prescriptions for adult outpatient visits for acute rhinosinusitis, authors reported nearly 2.8 million prescriptions per year along with a decrease in average cost per antibiotic prescription (from a range of US$ 59- US$ 125 to US$ 20-US$ 28) and estimated total annual cost of antibiotics (from a range of US$ 166-US$ 352 million per year to US$ 55.4-US$ 80.1 million per year) if guideline recommendations had been followed that would result in cost saving of US$ 51 million to US$ 297 million per year.[6]

Accordingly, more extensive integration of evidence-based guidelines on ABRS and AOM in the routine practice, development of national guidelines consistent with local antibiotic resistance patterns, and implementation of national educational programs and other measures to improve diagnostic and practice patterns of physicians seem crucial to enable improved management, justified use of antibiotics, change in societal expectations, decreased antibiotic resistance and potential economic benefits.[67,99,105]

Certain limitations to this study should be considered. First, being focused only on direct costs, and mainly antibiotic prescription costs, lack of data on indirect costs (loss of productivity due to the illness) or intangible costs of illness (costs of suffering for the patient and his/her family) seems to be the major limitation of the present study which likely to result in a downward bias in our estimates of the economic cost of ABRS and AOM. Second, use of epidemiological studies published to date rather than national database and use of expert consensus when guideline recommendations are not available to obtain data on practice patterns that were used to identify direct medical costs as well as treatment costs for different antibiotic initiation strategies might raise a concern with the validity and reliability of the data. Third, the treatment tree model was based on otherwise healthy pediatric and adult patients with AOM or ABRS, patients with chronic diseases or complications due to previous AOM or ABRS were not considered were not considered in the output data on per patient clinical practice and guideline based annual treatment costs. Nevertheless providing cost estimates for ABRS and AOM separately for pediatric and adult patients populations and in clinical practice versus guideline-based management for the first time in Turkey, our findings represent a valuable contribution to the literature.

In conclusion, our findings indicate that ABRS and AOM pose a considerable burden to health economics in Turkey, with antibiotic prescription identified as the main cost driver. Given the likelihood of substantial cost savings by adherence to guideline recommendations and reduced antibiotic resistance, our findings emphasize the role of evidence-based national guidelines in limiting diagnosis and treatment uncertainties with better targeting of patients to be prescribed with antibiotics and in choosing more effective and economic therapeutic options and developing policies encouraging responsible use of antimicrobials in primary care and outpatient settings.

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