

Direct Medical Cost Assessment in the <2 Years-Old Hospitalized RSV+LRTI Patients

<2 Yaş RSV+ASYE Yatan Hastalarda Direkt Tıbbi Maliyet Değerlendirmesi

Şefika Elmas Bozdemir¹, Solmaz Çelebi², Deniz Çakır³, İsmail Özcan¹, Deniz Sığırlı⁴, Enes Salı⁵, Arife Özer², Mustafa Hacımustafaoğlu²

¹Clinic of Pediatrics, Bursa Dörtcelik Pediatric Hospital, Bursa, Turkey

²Department of Pediatric Infectious Diseases, Uludag University School of Medicine, Bursa, Turkey

³Clinic of Pediatric Infection, Umraniye Training and Research Hospital, İstanbul, Turkey

⁴Department of Biostatistic, Uludag University, School of Medicine, Bursa, Turkey

⁵Clinic of Pediatric Infectious Diseases, Sanliurfa Training and Research Hospital, Şanlıurfa, Turkey

Abstract

Objective: This multi-center study aimed to assess the direct medical costs in patients aged between 0-2 year-old admitted to the hospital due to lower respiratory tract infection (LRTI), which was identified as respiratory syncytial virus (RSV) in 3 big pediatric hospitals for a year.

Material and Methods: During one-year period, <2-year-old LRTI patients with RSV+ and RSV- were included in the study conducted in 3 different pediatric hospitals. RSV was diagnosed with the detection of nasopharyngeal antigen. Direct medical costs (hospitalization, laboratory and treatment costs) were removed from the hospitals bills. Antibiotic costs of the antibiotic-treated cases were calculated independently. The indirect costs in the study were not considered and evaluated.

Results: In the study, 10% of the total inpatients aged <2-years were hospitalized with LRTI. 38% (254/671) of patients with LRTI, 41% (151/368) of those with acute bronchiolitis and 34% (103/303) of those with pneumonia were RSV positive. 4% of all hospitalized cases were RSV+LRTI; nearly 88% of the RSV+LRTIs and 92% of RSV-LRTIs received antibiotics (p=0.09). 10% of the RSV+LRTIs and 13% of RSV-LRTIs were hospitalized in the intensive care units (p=0.19). It was found that the total direct medical hospitalization costs including the antibiotics including the RSV+LRTI median values were 334 (range: 6-21545) (mean+SD: 910±226) \$, antibiotic costs median value was 24 (0-7691) (103±548) \$, and non-antibiotic median value was 301 (6-18767) (789±1826) \$. It was found that these values in the RSV-LRTI, on the other hand, 358 (5-31938) (1028±2741) \$, 33 (0-33333) (90±236)

Özet

Amaç: Çok merkezli bu çalışmada, bir yıllık sürede 3 büyük çocuk hastanesinde 0-2 yaş arası Respiratuar Sinsityal Virüs (RSV) saptanan alt solunum yolu enfeksiyonu (ASYE) nedeniyle hastaneye yatırılan olgularda direkt tıbbi maliyet değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bir yıl süresince 3 farklı çocuk hastanesinde <2 yaş ASYE ile yatan RSV+ ve RSV- olgular çalışmaya alındı. RSV tanısı nazofarengiyal antijen tespiti ile konuldu. Direkt tıbbi maliyetler (yatış, laboratuvar, tedavi maliyetleri) hastane faturalarından çıkarıldı. Antibiyotik verilen olguların antibiyotik maliyetleri ayrıca hesaplandı. Çalışmada indirekt maliyetler dikkate alınmadı ve değerlendirilmedi.

Bulgular: Çalışmada toplam yatan <2 yaş olguların %10'u ASYE ile yattı. Yatan ASYE'lerin %38'i (254/671) akut bronşiyolitlerin %41 (151/368), pnömönilerin %34 (103/303) RSV pozitifiti. Tüm yatan olguların %4'ü RSV+ASYE idi RSV+ASYE'lerin yaklaşık %88'i RSV-ASYE'lerin %92'si antibiyotik almıştı (p=0,09). RSV+ASYE'lerin %10'u, RSV-ASYE'lerin %13'ü yoğun bakıma yatırıldı (p=0,19). Antibiyotik dahil toplam direkt tıbbi yatış maliyetleri RSV+ASYE'de kişi başı medyan değeri 334 (dağılım: 6-21545) (ortalama+ SD: 910±226) \$, olgu başına antibiyotik maliyeti medyan değeri 24 (0-7691) (103±548) \$, olgu başına antibiyotik dışı maliyet medyan değeri 301 (6-18767) (789±1826) \$ saptandı. RSV-ASYE'de ise bu değerler sırasıyla 358 (5-31938) (1028±2741) \$, 33 (0-33333) (90±236) \$, 320 (5-31767) (911±2625) \$ bulundu. RSV+ASYE olgularının %48'i 0-3 ay arasıydı ve bu yaş grubunda olgu başına maliyet ortalaması 4-6 ay ve 7-11 ay yaş gruplarına göre 2

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Correspondence
Address

Yazışma Adresi:
Mustafa Hacımustafaoğlu
E-mail:
mkemal@uludag.edu.tr

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\$, 320 (5-31767) (911±2625) \$ respectively. 48% of RSV+LRTI cases were aged between 0-3 months and it was found that the average cost per case was in this age group was two times higher than the 4-6 months and 7-11 months age group (on average 1068, 508 and 352\$ respectively). It was found that the hospitalization costs of the total of 254 RSV+ patients were \$ 231,178 and the costs of the 417 RSV- patients were \$ 428,991.

Conclusion: According to these results, RSV infections still constitute a significant part of RLTI at <2 years of age in our country and cause an important epidemiological and economic disease burden. (*J Pediatr Inf 2016; 10: 128-36*)

Keywords: Respiratory Syncytial virus, epidemiology, incidence, cost, Turkey, cost of disease burden

kattan daha fazla bulundu (sırasıyla ortalama 1068, 508 ve 352\$). Toplam 254 RSV+ olgunun yatış maliyeti 231.178\$, RSV- 417 olgunun maliyeti ise 428,991 \$ bulundu.

Sonuç: Bu sonuçlara göre RSV enfeksiyonları halen <2 yaşta ASYE'lerin önemli bir kısmını oluşturmakta ve önemli bir epidemiyolojik ve ekonomik hastalık yüküne neden olmaktadır.

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Anahtar kelimeler: Respiratuar sinsiyal virus, epidemiyoloji, insidans, maliyet, Türkiye, hastalık maliyeti

Introduction

Respiratory syncytial virus is the most common cause of lower respiratory tract infections in children under one year and constitutes a significant burden of disease (1). In the United States, RSV-related LRTI causes about 120,000 pediatric hospitalization annually, and this rate is rising steadily (2, 3). With the projection of the figures in the United States to the population in Turkey [The US population, as of April 2013, is 315,694,000 and the Turkish population is 75,627,384 as of December 2012], an average of 30,000 RSV-related hospitalizations in all age groups is estimated in our country (4, 5).

Respiratory syncytial virus is an important factor of LRTI in childhood period. In different regions of the world, RSV accounts for 12-52% in childhood acute bronchiolitis and pneumonia, 50-90% in acute bronchiolitis in <2 year-old cases, and 5-40% of the pneumonia cases (6). In the United Kingdom, it was found that RSV-related hospitalization rates at age of <2 was higher than that of influenza virus (14% and 3%, respectively) (7). It was found in different studies in Turkey that RSV was detected in 35-50% of children hospitalized with LRTI (6). In one study, it was found that the annual incidence of RSV LRTI at <2 years was 7.8 / 1000 (8).

Although RSV is a viral infection, differential diagnosis should be made in patients with RSV LRTI. It was reported that 15-75% of the patients with documented RSV infection were given antibiotics in different parts of the world (9-13). There is no study in our country on the use of antibiotics in patients with RSV LRTI.

Although the RSV+LRTI hospitalization costs are different in different countries of the world, it was reported to be \$538-1577 per patient, and generally it was found to be higher than the RSV-LRTI (14-16). In Turkey, there is also no study evaluating the costs of RSV+ RSV-related hospitalizations.

Respiratory syncytial virus can cause a significant disease economic burden across the country as it is a frequent infection. Every year, 62,500-100,000 RSV

bronchiolitis-related hospitalization only is reported in the United States under the age of 5 and the average annual cost is \$300 million (9). In Australia, the annual costs of RSV-related hospitalization in children under 5 years of age are estimated to be in the range of \$ 24-50 million for children under 5 years of age (17). In Turkey, there is no study regarding the relationship between RSV hospitalization costs and disease burden in children, either.

The present study aimed to determine the direct medical cost, including the antibiotic costs, in the cases hospitalized due to RSV+LRTI and investigate the effects of this on the economic burden of the disease.

Material and Methods

The city of Bursa is situated within the borders of the Marmara region in the northwest of Turkey. Bursa has a high level of industrialization in the country and is in the 6th place in terms of financial development according to 2010 data (18). Furthermore, health indices of Bursa are satisfactory in comparison to those of Europe (It was found that while the infant mortality rate was 16.7 / 1000 live birth in 2007 in Turkey, it was 6.7 / 1000 in Bursa). The present study as a multi-centered was conducted with the participation of 3 big pediatric hospitals located in the center of Bursa and when the polyclinic records of the outpatients were evaluated, it is estimated that these hospitals served approximately 80% of the population of the province. According to the 2008 data of the Turkish Statistical Institute (TSI), it was reported that the number of children ≤2 years living in the city center of Bursa was 48,600. The total bed capacities of the three participating hospitals in which the study was conducted was 350 during the study (according to the information obtained from the Bursa Provincial Health Directorate) and constituted 67.5% (350/523) of the total pediatric bed capacity in the Bursa city center. All the children <2 years of age (671 cases) admitted to the 3 big pediatric hospitals with the diagnosis of LRTI for one year were included in the study (Uludag University School of Medicine, Pediatric Infectious

Diseases Clinic, Bursa Dörtçelik Pediatric Hospital, Private Doruk Medical Center).

Neonates and infants <3 months of age with the diagnosis of LRTI, and all children ≤ 2 years of age with a diagnosis of LRTI plus impaired general state or fever $\geq 40.5^{\circ}\text{C}$, extensive crepitations, apnea, and dyspnea or tachypnea (respiratory rate (RR) ≥ 60 /minute for neonates, ≥ 50 for infants 1-11 months and ≥ 40 for infants 12-24 months) who were hospitalized were eligible. Infants with extended sibilant rhonchi and prolongation in expiration on auscultation were defined as acute bronchiolitis. Infants with extended crepitations on auscultation and bronchopneumonic infiltration in posteroanterior (PA) lung X-ray without sibilant rhonchi and prolongation in expiration were defined as pneumonia. The cases of <2 years of age participating in the study were divided into age groups of; 0-3 months, 4-6 months, 7-11 months, and 12-24 months. The RSV antigen assignment in nasopharyngeal secretions of patients was assessed by an experienced physician or nurse using the RSV Respi-Strip kit from Coris BioConcept in the first 48 hours after the patient was hospitalized.

Hospital bills of the inpatient infants aged ≤ 2 years due to LRTI were obtained from the information processing records of the bills of the three hospitals and the billing information records of each patient were added to the research form with details. In the present study, the costs were considered only within the scope of direct (direct) medical costs; the direct medical costs assessed in the study included; only the hospital, bed, laboratory tests (excluding the RSV antigen test) and treatment costs covered by the SSI (Social Security Institution) within the reimbursement scheme; the antibiotic costs were calculated separately amongst the direct medical costs. RSV antigen test cost (approximately 6 USD=10.8 TL) was not in the SSI reimbursement scheme, so they were not included in the direct medical costs in the study. The direct non-medical costs were not assessed in this study. The costs were calculated separately for RSV+ and RSV- cases. For the study, approval numbered 2010-2 / 34 was received from the Ethics Committee of Clinical Investigations of Uludağ University School of Medicine on 11 October 2010.

The costs associated with the diseases can be *direct (medical and non-medical)* or *indirect (secondary)* costs. *Direct medical costs* are considered as; telephone consultations, consultations in outpatient clinics (primary care / home visits, emergency room evaluations), physician, hospital admission and laboratory diagnosis and treatment costs; other direct non-medical costs include the diaper costs during the hospitalization of the child. Only limited direct medical costs that could be billed such as hospital bed, laboratory or medical therapy were included

in the study. *Indirect costs* are considered as; the decrease in the quality of life of the family and the stress they experience included within the costs of many economic and social losses such as the lost working days by the parents and those caring the child, loss of earnings such as the cost of the lost working days and the child care costs, loss of working time and looking after the sick children (1, 19). In this study, the indirect costs and some medical costs (such as telephone calls, consultations, specialist visit fees, and faculty emergency pre-admission policlinic examinations and laboratory fees, patient subsidies, materials and medicines not covered by the SSI within the reimbursement scheme) were not taken into account.

Statistical analysis

The data were tabulated in the Microsoft Excel and the statistical evaluations were performed using the Statistical Package for the Social Sciences Statistics for Windows 20.0 (SPSS Armonk, NY: IBM Corp.) statistical package program. Actual p values were used and if the p value obtained was less than 0.05, the result was considered as significant. Non-normal variables were presented as median (minimum-maximum). Categorical variables were given with frequencies and percentages. Pearson chi-square test was used to compare categorical variables.

Results

A total of 671 patients aged ≤ 2 -year-old who were hospitalized due to LRTI in one year in 3 hospitals in the Bursa city center were included in the study. In the three hospitals in the province of Bursa where the study was conducted, the annual number of ≤ 2 years of hospitalized patients was 6350 during the year in which the study was conducted. The cases hospitalized with the LRTI constituted 10.56% (671/6350) of all ≤ 2 year-old hospitalized cases. The ages of the patients varied between 11 days to 24 months. 38% (254/671) of hospitalized LRTIs, 41% (151/368) of the acute bronchiolitis cases and 34% (103/303) of the pneumonia patients were RSV positive. Totally, 4% of all hospitalized cases were RSV+LRTI.

Antibiotic administration was evaluated in the patients, and it was found that there was no significant difference between the initial antibiotic administration rates of RSV+LRTI (88%) and RSV-LRTI (92%) (Table 1). There was no significant difference between RSV+A.bronchiolitis and RSV+pneumonia cases (85% and 92%, respectively) ($p = 0.099$) and again the antibiotic administration between the RSV+A.bronchiolitis and RSV+pneumonia cases (90.3% and 94.0%) ($p = 0.165$). After documentation of the RSV positivity, antibiotic administration decreased to 31% of the RSV+LRTIs.

Table 1. Antibiotic administration status of the inpatients with RSV+ and RSV-LRTI

	RSV+ n/N (%)	RSV- n/N (%)	p
Acute bronchiolitis	129/151 (85)	196/217 (90)	p=0.151
Pneumonia	95/103 (92)	188/200 (94)	p=0.557
Total LRTI	224/254 (88)	384/417 (92)	p=0.093

When the cases were evaluated in terms of their monitoring in the intensive care unit, it was found that 12% of all cases (83 cases) were monitored in the intensive care unit during the treatment. 10% (26 cases) of RSV+ cases and 13% (57 cases) of RSV-related cases received intensive care support and there was no statistically significant difference between them (p=0.190). Similarly, no significant difference was found between the

Table 2. Per-case evaluation of the average antibiotic, non-antibiotic and total direct medical costs of the patients hospitalized with LRTI (With the equivalent of TL, \$)*

	n/N %		Antibiotic cost / Per case	Total cases' cost of antibiotics	Non-antibiotic cost / per case	Total non- antibiotic cost	Cost of hospitalization/ per case	Total direct medical hospitalization cost
RSV+A.br	151/671 22.5%	TL	40 (0-13 844)	27 950	541 (11-23 675)	198 383	602 (11-37 519)	234 880
		\$	185±1176		1313±2830		1555±3826	
			22 (0-7691)	15 396	300 (6-13152)	109 284	334 (6-20843)	129 389
			101±653		723±1572		856±2125	
RSV+pneu	103/671 15.2%	TL	56 (0-5000)	19 652	545.5 (30-33 781)	164 614	604.5 (41-38 781)	184 133
		\$	190±643		1598±3848		1787±4423	
			31 (0-2777)	10 825	303 (30-18767)	90 681	335 (22-21545)	101 433
			105±357		880±2137		984±2457	
RSV-A.br	217/671 32.5%	TL	61 (0-2773)	41 815	596 (9-57 181)	412 560	700 (9-57 489)	457 349
		\$	192±401		1901±6038		2107±6170	
			33 (0-1540)	23 035	331 (5-31767)	228 921	388 (5-31938)	251 941
			106±222		1 047±3354		1161±3427	
RSV-pneu	200/671 29.8%	TL	60 (0-60 000)	26 240	544.5 (30-23 722)	276 560	616 (32-23 978)	320 740
		\$	131±452		1382±2607		1603±3045	
			33 (0-33333)	14 454	302.5 (16-13178)	152 349	342 (17-13321)	176 687
			72±251		761±1448		883±1691	
RSV+LRTI	254/671 37.9%	TL	44.5 (0-13 844)	47 625	542 (11-33 781)	363 804	602 (11-38 781)	419 658
		\$	187±988		1 432±3288		1652±4078	
			24 (0-7691)	26 235	301 (6-18767)	200 409	334 (6-21545)	231 178
			103±548		789±1826		910±2265	
RSV-LRTI	417/671 62.1%	TL	60 (0-60 000)	68 137	577.5 (9-57 181)	689 801	646 (9-57 489)	778 747
		\$	163±426		1 654±4726		1867±4935	
			33 (0-33333)	37 534	320 (5-31767)	379 993	358 (5-31938)	428 991
			90±236		911±2625		1028±2741	
All the cases in the study	671/671 100%	TL	55 (0-13 844)	115 412	549 (9-57 181)	1 052 530	626 (9-57 489)	1 197 332
		\$	172±698		1 568±4228		1784±4621	
			30.5 (0-7691)	65 577	305 (5-31767)	579 810	347 (5-31938)	659 578
			95±387		864±2348		982±2567	

*: Exchange rate; Mid-2012 Turkish Central Bank' exchange rate was considered; 1\$=1.8 TL, 1€=2.3 TL.

Data presented as median (minimum-maximum) in the first line as TL, in the third line as dollar, mean±standard deviation in the second line as TL, in the fourth line as dollar.

Table 3. Evaluation of Turkish Lira and US Dollar based costs of the cases hospitalized with RSV+LRTI and RSV-LRTI according to the age groups*, **

Age group	RSV+LRTI n=254				RSV-LRTI n=417				Total LRTI (RSV+and RSV) N=671						
	n/N %	TL \$	Antibiotic cost TL/\$	Non-antibiotic cost TL/\$	Total cost L/\$	n/N %	TL \$	Antibiotic cost TL/\$	Non-antibiotic cost TL/\$	Total cost TL/\$	n/N	TL \$	Antibiotic cost TL/\$	Non-antibiotic cost TL/\$	Total cost TL/\$
0-3 months	123/254 48.4%	TL \$	50 (0-5000) 161.4±587.6 27.78 (0-2777) 88.9±32.64	656 (11-33781) 1713.7±3723 364 (6-18767) 944.0±1818.33	700 (11-38781) 1938.8±4268.5 388 (6-21545) 1068±2371.4	134/417 32.1%	TL \$	79 (0-6000) 184.5±596.3 43 (0-3333) 101.6±331.28	789 (16-57181) 2216.2±5909.5 438 (8-31767) 1220.8±3283.06	857 (16-57488) 2544.4±6213.7 476 (8-31937) 1401.6	257/671% (383.3)	TL \$	63.5 (0-6000) 173±590.8 35 (0-3333) 95.2	684 (11-57181) 1965±4934.6 380 (6-31767) 1082.4	776 (11-57489) 2241.6±5327.8 431 (6-31938) 1234.8
4-6 months	54/254 21.2%	TL \$	40 (0-700) 72.2±111 22 (0-388) 39.7±61.67	527 (100-4599) 850±971.4 292 (55.5-2555) 468.2±823.22	577 (100-4890) 922.3±1042.7 320 (55-2716) 508±579.28	92/417 22.0%	TL \$	65 (0-2773) 205.8±398 36 (0-1540) 113.3±221.11	526 (9-57181) 1911.2±6348.6 292 (5-31767) 1052.8±35.27	623 (9-57488) 2121±6458.6 346 (5-31937) 1168.4	146/671 (21.7)	TL \$	55 (0-2773) 156±328 30 (0-1540) 85.8	526.5 (9-57181) 1515±5076.2 292 (5-31767) 834.6	590 (9-57488) 1673.6±5174.3 327 (5-31937) 921.9
7-11 months	43/254 16.9%	TL \$	35 (0-600) 67.3±97.8 19.4 (0-333) 37.0±54.33	397 (30-2581) 563.9±501.5 220 (16-1433) 310.6±278.61	492 (41-2802) 640.2±562.8 273 (22-1566) 352.6±312.67	90/417 21.5%	TL \$	44 (0-1300) 111±200.8 24 (0-722) 61.1±111.56	515 (9-4933) 898±1035.5 286 (5-2740) 494.6±	594 (9-5610) 1014.7±1145 330 (5-3116) 558.9	133/671 (19.8)	TL \$	44 (0-1300) 96.6±174.4 24 (0-722) 53.2	492 (9-4933) 787.5±906.4 273 (5-2740) 433.8	589 (9-5610) 891±1004.2 327 (5-3116) 490.7
12-24 months	34/254 13.3%	TL \$	49 (0-13844) 695±2609.9 27 (0-7691) 382.8±1.45	538 (200-23675) 2661.2±5499 298 (111-13152) 1465.9±3055	611 (210-37519) 3354.3±772.8 339 (116-20843) 1847.7±4318.22	101/417 24.2%	TL \$	52 (0-2540) 143.8±339.5 28 (80-1411) 79.2±188.61	539 (44-17626) 1386.8±2940.7 299 (24-9792) 763.9±	615 (44-20166) 1545.8±3142.7 341 (24-11203) 851.5	135/671 (20.1)	TL \$	50 (0-13844) 273.5±1304.5 27 (0-7691) 150.6	539 (44-23675) 1686.6±3656.4 299 (24-13152) 929.1	615 (44-37519) 1971.4±4685.2 341 (24-20843) 1085.9
Total	254/254 100%	TL \$	44.5 (0-13844) 187.5±988.6 24.7 (0-7691) 103.2±549.22	542 (11-33781) 1432.2±3288.7 301 (6-18767) 789.0±1827.05	602 (11-38781) 1652.2±4078.9 334 (6-21545) 910.1±2266.05	417/417 100%	TL \$	60 (0-6000) 163.4±426.9 33 (0-3333) 90.0±237.17	577.5 (9-57181) 1664.2±4726.7 320 (5-31767) 911.2±	646 (9-57489) 1867.5±4935.1 358 (5-31937) 1028.7	671/671 (100)	TL \$	55 (0-13844) 172.7±698.6 30 (0-7691) 95.1	549 (9-57181) 1568.6±4228.6 305 (5-31767) 864	626 (9-57489) 1784.4±4621.3 347 (5-31938) 982.9

*: Exchange rate; Mid-2012 Turkish Central Bank exchange rate was considered; 1\$=1.8 TL, 1€=2.3 TL.

** : Figures are stated as average

Data presented as median (minimum-maximum) in the first line as TL, in the third line as dollar, mean±standard deviation in the second line as TL, in the fourth line as dollar.

RSV or RSV-acute bronchiolitis and / or pneumonia in terms of admission to the intensive care unit.

Direct medical hospitalization costs of the patients including antibiotics were evaluated. Direct medical costs included the physician, hospital admission and laboratory diagnosis and treatment costs. Table 2 illustrates the comparison of the median value of antibiotic, non-antibiotic and total direct medical costs of RSV+LRTI and RSV-LRTI cases. The costs were based on hospital bills. Because of some patients with green card, their costs are free of charge (paid by the government so their bills reveals zero) and their cost are as "0". Because of wide range of the costs, non-normal variables were presented as mainly median (minimum-maximum) for statistical analysis.

Direct medical hospitalization costs of the patients including antibiotics were evaluated. Direct medical costs included the physician, hospital admission and laboratory diagnosis and treatment costs. It was found that the antibiotic costs of the cases with RSV+LRTI during their hospitalization (median value 24 (0-7691) \$), were lower than the antibiotic cost of the cases with RSV-LRTI, 33 (0-33333) \$ (p=0.002). When the non-antibiotic costs of the cases were compared, it was found that the median value was 301 (6-18767) \$ in the cases with RSV+LRTI and 320 (5-31767) \$ in the patients with RSV-LRTI and there was no statistically significant difference between them (p=0.428). When the total direct medical costs were compared, it was found that median value was 334 (6-21545) \$ in the patients with RSV+LRTI and 358 (5-31938) \$ in the patients with RSV-LRTI and there was no statistically significant difference between them (p=0.228).

When the cases with RSV+A. bronchiolitis and RSV+ pneumonia were compared in terms of their antibiotic initiation (85.4% and 92.2%) it

was found that there was no statistically significant difference between them ($p=0.099$). Similarly, when the RSV-A bronchiolitis and RSV-pneumonia cases were compared in terms of their antibiotic initiation (90.3% and 94.0%) there was no statistically significant difference between them ($p=0.165$).

The distribution of the cases according to age groups and their costs (antibiotic costs, non-antibiotic costs and the total cost) were calculated (Table 3). Approximately half of the RSV+LRTI cases (48.4% 123/254) were detected in the 0-3 month group. In the patients under three months, it was found that both antibiotic and non-antibiotic costs per case were two or more times higher than the 4-11-month group.

Discussion

Knowing the economic burden of the illness caused by the common illnesses in the society is initially beneficial for determining the strategies and helps to solve the health problems in an efficient manner. RSV is the most common cause of acute bronchiolitis and viral pneumonia in patients under 2 years of age, and usually 1-2% or less of the patients requires hospitalization (20). Nonetheless, the LRTIs that cause hospitalization in children <2 years of age in the world, are among the leading factors with a 17.5-66% detection rate including the developed countries (8). It was found that the incidence of annual hospitalization for RSV LRTI under the age of 5 years in the world was 1.3-31.2 / 1000 in the community, and the highest hospitalization rates were in the children under 1 year of age (8).

Costs of the inpatient cases included *direct (medical and non-medical)* and *indirect (secondary)* costs and the consequential individual and social costs. *Direct medical costs were calculated as*; the telephone consultations, the consultations in the outpatient settings (primary care / home visits, emergency room assessments), physician, hospital admission and laboratory diagnosis and treatment costs, laboratory, antibiotics and other drug treatment costs.

Direct medical costs included; telephone consultations, consultations in the outpatient settings (primary care / home visits, emergency room assessments), physician, hospital admission and laboratory diagnosis and treatment costs; in the present study, the direct medical costs were calculated as only the bed cost, laboratory, antibiotics, and other drug treatment costs. Physicians' visits, consultations, medicines and medical care materials used in patient care and not covered by the social security institution were not included in the direct medical cost calculation. Direct non-medical costs, on the other hand, included the diaper costs during the hospitalization

of the child etc. and the costs were excluded from the study. *Indirect costs* were considered as; the decrease in the quality of life of the family and the stress they experience included within the costs of many economic and social losses such as the lost working days by the parents and those caring the child, loss of earnings such as the cost of the lost working days and the child care costs, loss of working time and looking after the sick children (1, 19). The indirect costs were not taken into account in this study. Within this framework, taking into account the other medical direct and indirect costs and indirect costs spent per patient, it is possible to predict that disease burden of the hospitalized cases will be higher than calculated.

In the United States, RSV-related LRTI causes about 120,000 children to be hospitalized annually, and this rate is rising steadily (2, 3). With the projection of the figures in the United States to the population in Turkey [The US population, as of April 2013, is 315,694,000 and the Turkish population is 75,627,384 as of December 2012], an average of 30,000 RSV-related hospitalizations in all age groups is estimated in our country (4, 5). In a study conducted in Turkey, it was estimated that only 18,800 children under 2 years of age would be hospitalized due to RSV LRTI (8). Considering that the annual cost of hospitalization for RSV in the US was \$ 300 million, it can be estimated that with a rough estimate based solely on the population, approximately \$ 75 million cost of RSV LRTI per year (all ages) in Turkey might occur. The rate of RSV-related hospitalization in Australia was reported as 2.2-4.5 / 1000 at <5 years and 8.7-17.4 / 1000 at <1 year, and the direct cost of these annual hospitalizations was estimated to be around \$ 24-50 million (17). In a study conducted in Turkey, it was found that the RSV+LRTI hospitalization rate at <2 years was 7.8 / 1000 (8). Considering that RSV LRTI rates were similar, it is possible to assume that the cost of <5 years old RSV-LRTI in Turkey would be at least 100 million dollars in comparison with the Australian population (approximately 23 million, 2013) and Turkey's population (75 million, 2013). Assuming that the average hospitalization cost of our inpatient RSV+LRTI cases was \$ 910 and that there was approximately 18,800 <2 years old RSV LRTI hospitalization in Turkey, it is possible to estimate that the total cost of <2 years of hospitalization across the country will be over \$17 million. When all the 2-years of age patients, all other medical costs and indirect costs are added up to this estimated cost, it is thought that the economic burden of disease will be much higher.

RSV is usually a benign disease, and patients with acute bronchiolitis usually do not require hospitalization, however, of hospitalized patients 6-9 of them requires ICU care in our study, in RSV+LRTI patients, the rate of ICU care was 10% and it was found to be comparable with the

RSV-LRTI cases 13%), it was consistent with the literature. ICU care can be a factor that increases the cost of patients (21, 22).

Acute bronchiolitis can be caused by different viruses such as RSV, rhinovirus, metapneumovirus, adenovirus, parainfluenza virus and influenza virus. There can be also co-infections, mostly together with RSV. More than one virus associated LRTIs can account up to 2/3 of the cases (21, 23-27). Some studies conclude that co-infections cause more severe LRTIs (23,25), however some other studies not (28, 29). We could not evaluate the other viruses except RSV; this is a limitation of our study.

There is a wide distribution of the costs in our patients. Some patients had zero cost (because of no legally cost charging to some patients as mentioned before), some patients had low cost due to non-serious disease and discharging in a few days. However, some critical serious patients requiring ICU had high costs. This wide distribution can cause some problems interpreting the statistical analysis, and can be another limitation of our study.

Antibiotic administration is not recommended in RSV LRTI. However, antibiotics can be given if the bacterial agent cannot be clearly distinguished, especially in serious cases. It was reported that 15-75% of antibiotics were given to the patients in different countries of the world hospitalized due to RSV infection (9-13). In a study in Germany in which 0-16-year-old children hospitalized due to respiratory tract infection for 4 years between 1996 and 2000 were evaluated, it was reported that 65% of the cases were given antibiotics (11). In a study conducted in Qatar, it was reported that 49.4% of the cases were started antibiotics (12). In a study involving 152 patients with RSV+LRTI in Canada, it was reported that 67% of patients had antibiotics before hospitalization, and 60.5% of cases during admission and 75% of patients in total had antibiotics (13). In Turkey, there is no study on the use of antibiotics in RSV LRTI. Since there is no assessment of the use of antibiotics in studies conducted in Turkey, no comparison has been made. In our study, a higher rate (88%) of antibiotic treatment was initiated in our RSV+patients than in Germany and Canada, but following the detection of RSV+, antibiotic treatment was discontinued in 68% of the cases. Bacterial growth was detected in the blood culture of only 4 cases (5%) that were continued the antibiotic therapy considering co-infection. Antibiotic use is not recommended in A. bronchiolitis since it is generally a viral syndrome. Our antibiotic rates were high in the RSV+LRTIs. This may be explained by the severity of the case with possible bacterial infections. Although the antibiotic use decreased to 31% after documentation of the

RSV positivity, this rate was still high. It is obvious that there was still unnecessary antibiotic treatment in the follow-up of the RSV+LRTIs in our hospital, which was cost-enhancing and might lead to additional complications; this was another important limitation of our study.

In a study conducted in the United Kingdom, it was found that the total cost of hospitalization for children under ≤ 2 years of age with bronchiolitis was £542 203 (our estimation; £830 per patient, or \$1276 per patient), while it was calculated that the cost of hospitalization for 411 children with RSV+acute bronchiolitis ≤ 2 years was £421 938 (our estimation; £1026/patient) (14). (In June 2012, according to the currency rate of the Turkish Central Bank, £1= \$1.5378) (30).

In a study conducted in Jordan, it was found that 64% of patients with LRTI had RSV positivity and in comparison to the cost of hospitalization, the RSV+cases caused more financial burden than RSV-cases (\$538 and \$431, respectively) (15). In another study, the 2-year-long health expenditures of 20 cases admitted due to RSV+RTI of out the premature infants born 32-35 weeks were compared with 30 infants admitted due to RSV-RTI and similarly with 108 infants without RTI, it was reported that the health expenditures in the RSV+group were significantly higher than the other two groups (16). In our study, it was found that the average direct medical hospitalization cost of a patient with RSV+LRTI was \$910 and that of a RSV-patients \$1028 ($p > 0.05$) and in contrast to the studies mentioned above, RSV+LRTI costs were not higher than RSV-LRTI (Table 2). In regard of the cost of antibiotics as median values, in RSV+LRTI was found to be also lower than in RSV-LRTI, this is consistent with the expectation.

According to the World Bank data, gain per capita in Turkey (\$10.851) was lower than the UK (\$38.929) and comparable with Jordan (31-33). The average cost of our hospitalized RSV+LRTIs cases was found lower than the UK. However, when compared with Jordan, it is seen that the hospital costs for RSV+cases were similar to those in our country. However, it should be born in mind that we calculated only the limited direct medical hospital costs such as bed, laboratory except RSV testing and medical therapies. When the average cost of the patients according to the age groups was evaluated, it was found that the highest costs were in 0-3 month infants with a cost of \$ 1,068 per patient.

Our study revealed that RSV was a significant burden of disease cost for the hospitalization of children aged ≤ 2 . It is possible to say that our findings are comparable to those of the developed and developing countries. The fact that our RSV+LRTI cases were composed of healthy < 2 year old infants rather than the risk groups also shows that vaccination will be very important in protection against this disease.

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