The Armenian SORT IT Course

Respiratory syncytial and influenza virus detecting rapid tests in children younger than 5 years of age in Armenia

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Abstract

Introduction: Acute respiratory infections (ARIs) are major causes of morbidity in early childhood. They are mainly caused by viruses, including influenza (INF) and respiratory syncytial viruses (RSV). We aimed to investigate the role of RSV and INF in children hospitalized for ARIs and to show the impact of RSV/INF rapid testing on management of patients.

Methodology: Cross-sectional study using data of inpatient care of children younger than five years hospitalized in Arabkir Medical Center due to ARI from November 1, 2013 to April 1, 2014. Nasopharyngeal swabs were tested for RSV and INF types A and B by direct antigen detection tests.

Results: A total of 915 patients, 583 (63.7%) boys and 332 (36.3%) girls were included in the study with the mean age of 18.8 ± 16.3 months. Among them, 390 (42.6%) were tested positive, 3 (0.3%) subjects tested positive both for RSV and INF: 269 (29.4%) for RSV and 124 (13.6%) for INF (A – 121, B – 3). Out of 915 children, 209 (23%) were pretreated with antibiotics, most often with oral amoxicillin/clavulanic acid (n = 54, 25.8%), sulfamethoxazole/trimethoprim (n = 46, 22%), and amoxicillin (n = 38, 18.2%), followed by intramuscular ceftriaxone (n = 37, 17.7%).

Conclusions: The usage of antigen tests for detection of respiratory viruses allowed to document high rates of RSV and INF in children admitted to the hospital. In settings where polymerase chain reaction method is not readily available, implementation of rapid tests for detection of respiratory viruses is important in the management of pediatric patients including cohorting and more targeted use of antibiotics.

Introduction

Respiratory tract infections are the most common diseases of infants and young children often caused by respiratory syncytial virus (RSV) and influenza (INF) type A and type B.

Respiratory syncytial virus is a leading cause of acute respiratory infections (ARIs) in patients of all ages. Infants are infected during the first year of life, with nearly all having been infected at least once by the second birthday. Most RSV-infected infants experience upper respiratory tract symptoms, and 20-30% develop lower respiratory tract disease with their first infection. Virtually all children have serologic evidence of RSV infection by 2 years of age. Nevertheless, previous RSV infections do not provide protection against reinfections [1].

Children younger than 5 years of age, especially those younger than 2 years old, are at high risk of serious INF related complications, hospitalization, emergency department visits and death [2,3].

The clinical manifestations of viral infections are often indistinguishable from ARIs of other etiologies. Overlap of symptoms between viral and bacterial infections may lead to inappropriate antibiotic prescriptions, leading to the development of resistant bacterial species, which is a nowadays of ever greater importance [4]. Hence, accurate and timely laboratory testing is needed to guide clinical management.

Among the methods that have been developed to diagnose viral pathogens, cell cultures are complicated, expensive, and time consuming. Although, the polymerase chain reaction (PCR) method is widely used for detection of respiratory pathogens because of its high sensitivity and specificity, rapid antigen detection tests (RADTs) remain practical tools for the detection of respiratory viruses in clinical practice.

Antigen-based assays are inexpensive and easy to perform [5,6]. Additionally, due to its high cost, the PCR method is not readily available in developing countries with limited resources such as Armenia.

Despite the public health concern about the role of RSV- and INF-induced infections among children, there have been no any publications available in Peer review journals so far concerning the situation in Armenia.

The aim of this study was to investigate the impact of rapid RSV/INF detection on the management of 0-5 year-old patients hospitalized with ARIs.

In a tertiary level children's hospital in Yerevan, Armenia, for the period of November 2013-April 2014, we determined: a) incidence and clinical course of RSV and INF in hospitalized children; b) prescription patterns of antibiotics and systemic steroids in RSV-/INF-positive and -negative groups.

Methodology

Study Design

Cross-sectional study based on the inpatient care data from the Arabkir Joint Medical Center (JMC), a tertiary level children's hospital in Yerevan, Armenia.

Study setting

General: Armenia is an ex-Soviet developing country, located at the crossroads of Europe and Asia. About a fifth of its 3-million population is under 18 years of age [7,8].

Specific: Arabkir JMC is one of the three biggest tertiary level children's hospitals of Armenia, where patients can apply directly or be referred from primary and/or secondary healthcare facilities. It serves around 15.000 inpatients and up to 100.000 outpatients annually.

Antibiotics have always been related to prescription drugs in Armenia, however, the requirements were not met in full force. Citizens of the country were getting antibiotics without prescriptions at the pharmacies. Since March 1, 2018 in Armenia, according to the updated regulations, pharmacies are obliged to release antibiotics only on prescription of a doctor.

Study site, population and period

The study was conducted from November 1, 2013 to April 1, 2014 in Arabkir JMC and included 0-5-years-old patients with symptoms of ARI. Study patients were prospectively tested for the RSV, INF-A and INF-B infections using OSOM® tests (Sekisui Diagnostics, San Diego, USA): immunochromatographic assay for the qualitative detection of viral antigens from nasal swab or nasal suction specimens. Nasopharyngeal swabs, sampled in universal virological transport tube, were taken when the patient was admitted with the symptoms of ARI. Only the patients who had an OSOM® RSV/INF A, B test and parental/care-giver consent were included in the study. Exclusion criteria were duration of fever for more than 7 days (low probability of viral infection), and antibiotic pre-treatment for more than 3 days (to allow evaluation of possible secondary bacterial complications and needs of antibiotic prescription).

Data collection, sources and statistical analysis

Data were extracted from patients' medical records using data collection sheet, specifically developed for this purpose. Abstracted data was entered into Microsoft Access electronic database for analyses. Variables collected included the following sociodemographic and clinical characteristics: age, gender, oxygen saturation, presence or absence and duration of fever and respiratory symptoms, final diagnosis, chest radiography interpretations, common blood count results and C-reactive protein levels, prescribed antibiotics, hospitalization units (general pediatric ward, intensive care unit) and length of hospitalization. Data were analyzed using the STATA software (Version 12). After conducting descriptive analyses (means, medians, standard deviations, and frequencies), the χ^2 test or non-parametric Fisher's exact test, as appropriate, was used to test differences in proportions of independent variables between RSV-/INF-positive and RSV-/INF-negative groups. The mean differences in different groups were tested using Student's *t*-test. The level of significance was set at 5%.

Ethics Approval

The study was approved by the Institutional Review Board of the Yerevan State Medical University, Armenia.

Results

A total of 915 patients, including 583 (63.7%) boys and 332 (36.3%) girls were included in the study. Their mean age was 18.8 ± 16.3 months. Positive test was recorded in 390 (42.6%) patients, with 3 (0.3%) subjects tested positive both for RSV and INF: 269 (29.4%) for RSV and 124 (13.6%) for INF (INF A – 121 and INF B – 3), respectively. Half of admitted children (n = 460, 50.3%) were self-referred evading their primary care facilities.

Among 915 children, 209 (23%) received pretreatment with antibiotics: the most commonly were

oral amoxicillin/clavulanic acid (n = 54, 25.8%), sulfamethoxazole/trimethoprim (n = 46, 22%), and amoxicillin (n = 38, 18.2%), followed by intramuscular ceftriaxone (n = 37, 17.7%).

Demographic data and clinical presentation of children with RSV and INF infection are summarized in Table 1 and Table 2, respectively.

The RSV infection manifested as bronchiolitis/acute obstructive bronchitis (AOB) and was associated with significantly increased rates of admission to intensive care unit (ICU) (13.38% versus 7.24%, p = 0.005) as well as increased rates of administration of steroids (51.7% versus 29.5%, p < 0.01). Cases of INF infection were more likely to present as uncomplicated ARI (82.26%) with hospitalization to general pediatric wards.

Although the rates of antibiotic prescriptions were unchanged during hospitalization, the trends of administred drugs were different. The most commonly used antibiotics in the RSV-positive group were ampicillin (25/79, 31.6%) and amoxicillin (21/79, 26.6%), while ceftriaxone (9/31, 29%) was at the top of prescriptions in the INF-positive group.

No case of invasive bacterial infection was documented during the study period.

Discussion

The present study documented the high rates of RSV (29.4%) and INF (13.55%) among hospitalized children under five years old with ARI in our hospital. Half of all included children avoided to visit their primary care institutions and were self-referred to the tertiary level hospital. This illustrates the importance of developing efficient mechanisms to enhance the "gatekeepers" function by reinforcing the network of primary care institutions.

We showed that RSV infection clinically manifested as AOB/bronchiolitis with predominantly respiratory symptoms on admission, increased

Table 1. Comparative demographic and clinical characteristics of RSV-positive and RSV-/INF-negative patients.

Variable	Total N = 794	RSV-positive N = 269	RSV-/INF-negative N = 525	Odds Ratio / Mean difference	95% CI	p value
Age, n (%)						
0-1 year	393 (49.5%)	83 (30.86%)	310 (59.05%)	3.23	2.37 – 4.41	< 0.01[2]
1-5 years[1]	401 (50.5%)	186 (69.14%)	215 (40.95%)	1	-	
Gender, n (%)						
Female	287 (36.15%)	101 (37.55%)	186 (35.43%)	0.91	0.67 – 1.24	0.56[2]
Male[1]	507 (63.85%)	168 (62.45%)	339 (64.57%)	1	-	-
Comorbidities, n (%)						
No	606 (76.32%)	209 (77.7%)	397 (75.62%)	0.89	0.63 – 1.26	0.52[2]
Yes[1]	188 (23.68%)	60 (22.3%)	128 (24.38%)	1	-	-
Pretreatment with antibiotics, n (%)						
No[1]	603 (75.94%)	191 (71%)	412 (78.48%)	1	-	-
Yes	185 (23.3%)	76 (28.25%)	109 (20.76%)	0.66	0.47 – 0.93	0.02[2]
Do not remember	6 (0.76%)	2 (0.74%)	4 (0.76%)	0.93	0.13 – 10.34	1[3]
Hospitalization ward, n (%)						
ICU	74 (9.32%)	36 (13.38%)	38 (7.24%)	0.51	0.31 – 0.82	< 0.01[2]
Pediatric[1]	720 (90.68%)	233 (86.62%)	487 (92.76%)	1	-	-
Antibiotic during hospitalization, n (%)						
No	570 (71.79%)	190 (70.63%)	380 (72.38%)	1.09	0.79 – 1.51	0.60[2]
Yes[1]	224 (28.21%)	79 (29.37%)	145 (27.62%)	1	-	-
Systemic steroids during hospitalization, n (%)						
No	500 (62.97%)	130 (48.33%)	370 (70.48%)	2.55	1.88 – 3.46	< 0.01[2]
Yes[1]	294 (37.03%)	139 (51.67%)	155 (29.52%)	1	-	-
Clinical diagnosis, n (%)						
ARI[1]	247 (31.11%)	4 (1.49%)	243 (46.29%)	1	-	-
Laryngotracheitis	57 (7.18%)	3 (1.12%)	54 (10.29%)	0.3	0.05 – 2.09	0.13[3]
Pneumonia with effusion	14 (1.76%)	1 (0.37%)	13 (2.48%)	0.22	0.02 – 11.34	0.24[3]
Pneumonia	74 (9.32%)	30 (11.15%)	44 (8.38%)	0.02	0.01 – 0.07	< 0.01[3]
AOB / Bronchiolitis	402 (50.63%)	231 (85.87%)	171 (32.57%)	0.01	0 – 0.03	< 0.01[3]
Hospital stay in days, mean (SD)	8.66 (5.65)	8.82 (5.65)	8.58 (5.66)	-0.24 (0.42)	-1.13 – 0.64	0.59[4]

[1] Reference Group; [2] Pearson's Chi-Square test; [3] Fisher's exact test; [4] Student's t-test; AOB – acute obstructive bronchitis. ARI – acute respiratory infection. CI – confidence interval. ICU – intensive care unit. INF – influenza virus. RSV – respiratory syncytial virus. SD – standard deviation.

consumption of systemic steroids, longer hospital days and frequent hospitalization in ICU department.

Most INF cases were diagnosed as uncomplicated ARI. In the INF-positive group, ceftriaxone was the most commonly prescribed antibiotic and fever was reported as the main indication for its administration. No patient received any antiviral treatment such as zanamivir or oseltamivir.

The rate of RSV infection was similar to findings in Turkey (32%) – the western neighbor of Armenia, in contrast to studies in the southern bordering country Iran (19.4%) [9]. The incidence of INF infection in different countries is varying (10-40%) because of dissimilar preventive immunization programs [10,11].

The rate of antibiotic prescriptions during hospitalization was not different in RSV- and INF-positive and negative patients. However, the most commonly used antibiotics in the RSV-group were ampicillin and amoxicillin. This might be explained by the fact that the indications for administration of

antibiotics in RSV-positive patients were more targeted to otitis or pneumonia while children with INF (and high fever) rather were treated with ceftriaxone. This shift from WHO Watch group of antibiotics to Access group is one important step toward antimicrobial stewardship strategies [12].

We documented no case of invasive bacterial infection during the study. Possible explanation for this may be early administration of antibiotics in outpatient and hospital levels.

Previous studies from other countries found that rapid viral diagnosis leads to optimized clinical care, reduced antibiotic use, helps infection control and is cost effective [13-17].

We strongly advocate for implementation of the rapid point-of-care tests for detection of respiratory virus antigens in hospitals in countries with limited resources. This helps to identify the burden of respiratory viruses and has the potential to enhance rational management of patients admitted with

Table 2. Comparative demographic and clinical characteristics INF-positive and RSV-/INF-negative patients.

Variable	Total N = 649	INF-positive N = 124	RSV-/INF-negative N = 525	Odds Ratio / Mean difference	95% CI	p value
Age, n (%)						
0-1 year	397 (61.17%)	87 (70.16%)	310 (59.05%)	1.63	1.07 – 2.49	0.02[2]
1-5 years[1]	252 (38.83%)	37 (29.84%)	215 (40.95%)	1	-	-
Gender, n (%)						
Female	231 (35.59%)	45 (36.29%)	186 (35.43%)	1.04	0.69 – 1.56	0.86[2]
Male[1]	418 (64.41%)	79 (63.71%)	339 (64.57%)	1	-	-
Comorbidities, n (%)						
No	498 (76.73%)	101 (81.45%)	397 (75.62%)	1.42	0.86 – 2.32	0.17[2]
Yes[1]	151 (23.27%)	23 (18.55%)	128 (24.38%)	1	-	-
Pretreatment with antibiotics, n (%)						
No	512 (78.89%)	100 (80.65%)	412 (78.48%)	1	-	-
Yes[1]	133 (20.49%)	24 (19.35%)	109 (20.76%)	0.91	0.55 – 1.49	0.69[2]
Do not remember	4 (0.62%)	0 (0%)	4 (0.76%)	0	[0, 6.33]	1[3]
Hospitalization ward, n (%)						
ICU	45 (6.93%)	7 (5.65%)	38 (7.24%)	0.77	0.33 – 1.76	0.53[2]
Pediatric[1]	604 (93.07%)	117 (94.35%)	487 (92.76%)	1	-	-
Antibiotic during hospitalization, n (%)						
No	473 (72.88%)	93 (75%)	380 (72.38%)	1.14	0.73 – 1.79	0.56[2]
Yes[1]	176 (27.12%)	31 (25%)	145 (27.62%)	1	-	-
Systemic steroids during hospitalization, n (%)						
No	473 (72.88%)	103 (83.06%)	370 (70.48%)	2.05	1.24– 3.41	< 0.01[2]
Yes	176 (27.12%)	21 (16.94%)	155 (29.52%)	1	-	-
Clinical diagnosis, n (%)						
ARI[1]	345 (53.16%)	102 (82.26%)	243 (46.29%)	1	-	-
Laryngotracheitis	61 (9.4%)	7 (5.65%)	54 (10.29%)	0.31	0.14 – 0.7	< 0.01[2]
Pneumonia with effusion	15 (2.31%)	2 (1.61%)	13 (2.48%)	0.37	[0.04, 1.67]	0.25[3]
Pneumonia	53 (8.17%)	9 (7.26%)	44 (8.38%)	0.49	0.23 – 1.04	0.06[2]
AOB / Bronchiolitis	175 (26.96%)	4 (3.23%)	171 (32.57%)	0.06	0.01 – 0.15	< 001[3]
Hospital stay in days, mean (SD)	8.51 (5.63)	8.16 (5.52)	8.58 (5.66)	-0.42 (0.55)	-1.65 – 0.8	0.50[4]

[1] Reference Group; [2] Pearson's Chi-Square test; [3] Fisher's exact test; [4] Student's t-test; AOB – acute obstructive bronchitis. ARI – acute respiratory infection. CI – confidence interval. ICU – intensive care unit. INF – influenza virus. RSV – respiratory syncytial virus. SD – standard deviation.

respiratory infections. Timely identification of viruses can also be crucial for the cohorting of patients, especially during the winter season, when hospital beds are overloaded.

The study was conducted during the first season of implementation of RADTs. We anticipate that during the next seasons the use of laboratory tests, chest X-rays and antibiotics will be drastically reduced and further studies are necessary to assess their impact.

The study *strengths* include the selection of the largest tertiary level pediatric hospital as the study site and inclusion of all eligible hospitalized under-five patients with ARI across the study period. Data were sourced from patient files, double entered and validated and thus we believe robust, and we adhered to STROBE guidelines for the reporting of observational studies [18]. One of the main *limitations* of the study is that our data is restricted to one of the three tertiary level children's hospitals in the country. Another limitation is that the RADT results were not rechecked by PCR method. Notwithstanding these limitations, the study has a number of policy and practice implications. First of all it shows high rate of hospitalization due to RSV- and INF-infection. A high rate of influenza infection requires special attention and could be decreased by immunization of high-risk patients.

Second, the study raises the problem of patients evading their primary care facilities: half of the patients were self-referred. There must be a national effort to rethink how to practice primary care. Finally, the excessive use of antibiotics and overuse of third generation cephalosporins are issue in primary care facilities as well as in tertiary level hospital. That could be partially explained by the absence of national guidelines for the management of respiratory infections among children. This issue could be improved by implementation of guidelines and antibiotic stewardship programs by Ministry of Health.

Conclusion

In conclusion, the antigen tests for detection of respiratory viruses allowed documenting high rates of RSV and INF in children admitted to Arabkir JMC. In settings where PCR method is not readily available, implementation of rapid antigen tests for recognition of respiratory viruses is important. It will improve the management of patient cohorting, targeted use of antibiotics, and efficient use of other diagnostic methods and facilities.

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