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Respiratory Viruses in Adults With Community-Acquired Pneumonia

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Background: Use of nucleic acid amplification techniques has increased the identification of respiratory viruses (RVs) in adult patients with community-acquired pneumonia (CAP). The objectives of the present study were to identify RV in patients with CAP using three different sampling methods and to compare CAP virus proportions and types with two comparison groups.

Methods: The study population included 183 adult patients with CAP, 450 control subjects, and 201 patients with nonpneumonic lower respiratory tract infection (NPLRTI). Each participant was sampled by oropharyngeal swab, nasopharyngeal swab, and nasopharyngeal washing, and the samples were tested for detection of 12 RVs by multiplex TaqMan Hydrolysis probe-based real-time polymerase chain reaction (Integrated DNA Technology; Coralville, IA).

Results: At least one RV was identified in 58 patients with CAP (31.7%) compared with 32 (7.1%) in control subjects and 104 (51.7%) in patients with NPLRTI ($P < .01$ and $P < .01$, respectively). Coronaviruses were identified in 24 (13.1%) patients with CAP, compared with 17 (3.8%) in control subjects, and 21 (10.4%) patients with NPLRTI. Respiratory syncytial virus was identified in 13 (7.1%), four (0.9%), and seven (3.5%); rhinovirus in nine (4.9%), nine (2.0%), and 15 (7.5%); and influenza virus in eight (4.4%), two (0.4%), and 63 (31.3%) patients with CAP, control subjects, and patients with NPLRTI, respectively.

Conclusions: The proportion of RV involvement in CAP is higher than previously reported. The proportion of RV identified in healthy subjects is significantly lower than in CAP, but it is not zero and should be weighed when interpreting corresponding proportions among patients.

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Abbreviations: CAP = community-acquired pneumonia; LRTI = lower respiratory tract infection; NAAT = nucleic acid amplification tests; NPLRTI = nonpneumonic lower respiratory tract infection; NPS = nasopharyngeal swab; NPW = nasopharyngeal washing; OPS = oropharyngeal swab; RSV = respiratory syncytial virus; RV = respiratory virus

The etiologic association between an identified respiratory virus (RV) and community-acquired pneumonia (CAP) in a particular patient is not clear cut, making the use of the term “viral CAP” problematic.

An RV can be the principal or only cause of CAP, but it also can simply represent a factor that predisposes the respiratory tract to superinfection by another pathogen that is the primary cause of the pneumonia.¹

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In addition to these two possibilities, one should consider the possibility that the patient is an asymptomatic carrier of the RV without any relation to the CAP. Given these three possibilities, it is not surprising that no association has been found between the identification of an RV in adult patients with CAP and the clinical manifestations of the disease.²⁻⁴

The involvement of RV in CAP has been recognized for many years, but over recent years, this phenomenon has gained increasing research interest. This interest is manifested in the increase in the number

of publications on this subject and even more so in the higher frequency and broader spectrum of RV identified in adult patients with CAP in recently published papers compared with similar papers published in the past.²⁻⁶ The use of nucleic acid amplification tests (NAATs) for the identification of RV is a common factor in these recent studies. Today, researchers in this field agree that this technique greatly increases the ability to identify RV in clinical samples compared with traditional methods, such as serology, viral culture, and immunofluorescence.^{2-4,6-8} Furthermore, two important groups of RV, rhinovirus and coronavirus, only can be identified by NAAT.^{2,3,5,9,10}

The previous studies focused on identification techniques for RV while ignoring the effect of the sampling site and method on their yield. In addition, none of the recent studies included a control group of subjects without evidence of respiratory infection to facilitate a valid interpretation of the results. Thus, the objectives of the present study were (1) to identify RV in hospitalized adult patients with CAP using the NAAT technique and a combination of three sampling methods and (2) to compare the proportion and types of RV identified in patients with CAP in two comparison groups, one group of healthy subjects without evidence of respiratory infection and the other including adult patients hospitalized for nonpneumonic lower respiratory tract infection (NPLRTI).

MATERIALS AND METHODS

Study Population

The study population comprised three groups of subjects: one group of hospitalized patients with CAP, one group of hospitalized patients with NPLRTI, and a control group. The study was approved by the Helsinki Committee for research on human beings of the Soroka Medical Center (Beer-Sheva, Israel), and all participants gave signed informed consent to participate. The study was conducted over two winter periods, the first between November 1, 2004, and March 15, 2005, and the second between November 1, 2005, and April 15, 2006. To avoid a seasonal effect on the results, recruitment of patients and control subjects was simultaneous, and the number of subjects in the study arms was balanced weekly.

The two patient groups included patients who were hospitalized from the community in one of seven internal medicine departments of the Soroka Medical Center and who fulfilled the following four inclusion criteria: aged > 18 years; an acute febrile illness of no more than 1 week's duration; a cough that appeared or worsened over the week prior to hospitalization; and in the week prior to hospitalization, at least appearance or worsening of shortness of breath, sputum production, wheezing, chest pain or discomfort, or a combination of more than one of these. Exclusion criteria were: hospitalized from a nursing home and past documentation of COPD or an abnormal spirometry examination performed 6 to 8 weeks after hospitalization.

In each hospitalization, a chest radiograph was taken while the patient was still in the ED. For study purposes, a senior pulmonologist and a senior radiologist analyzed all radiographs independently each week. Any radiograph that was interpreted as

pneumonia by one or both experts was classified, at this stage, as suspected pneumonia, and only those patients underwent repeat radiographs at the clinic follow-up 6 to 8 weeks after hospitalization. The same experts separately analyzed the paired radiographs (acute and convalescence) of these patients. Pneumonia was diagnosed only if both experts independently reported a pulmonary infiltrate in the acute phase radiograph that disappeared or retreated significantly in the follow-up radiograph. Those cases in which the two experts did not agree were not considered pneumonia for the purpose of the study. In patients who died in the hospital, pneumonia was diagnosed if the presence of a typical infiltrate on hospital admission was seen on chest radiograph that was not present in a previous radiograph. At the data analysis phase of the study, the patients were divided into the CAP or NPLRTI groups according to the presence or absence of pneumonia. None of the patients in the NPLRTI group underwent chest CT scan, so negation of CAP was based solely on chest radiographs. In the majority of patients with NPLRTI, the indication for hospitalization was decompensation of chronic comorbid disease and deterioration in an elderly patient's general condition due to the infection. A minority of patients were hospitalized for social reasons.

The control group comprised ambulatory patients who came to one of the outpatient clinics of the Soroka Medical Center, agreed to participate in the study, and fulfilled all of the following three conditions: aged > 18 years; had no known chronic lung disease or a state of immunosuppression as indicated by medical documentation and in response to a direct question; and had no evidence in the month prior to hospitalization of febrile illness, a cough, a throat ache, hoarseness, a running nose, taking antibiotic medications, or pregnancy (definite or possible) as indicated by response to a direct question. For each of the participants, data were collected with regard to age, sex, smoking habit, and vaccination status.

Sampling

Three physicians who were trained specifically for the task took all the samples from the patients and control subjects. In all hospitalized patients, the samples were taken as close as possible to the time of admission and in no case more than 24 h later. Three consecutive samples were taken from each participant in the following order: oropharyngeal swab (OPS), nasopharyngeal swab (NPS), and nasopharyngeal washing (NPW). Details of each of the sampling methods can be found in our previous publication.¹¹

Detection of RVs

Each sample was tested in parallel in three test tubes for the following viruses: influenza A and B, parainfluenza 2 and 3, human respiratory syncytial virus (RSV), human metapneumovirus, rhinovirus, adenovirus, and coronaviruses 229E, HKU1, OC43, and NL63. The sets of primers and probes used to detect the 12 viruses by multiplex hydrolysis probes-based real-time polymerase chain reaction, together with other technical details on detection, also can be found in our previous publication.¹¹

Statistical Analysis

Sample size calculations for this study were based on data collected in a preliminary phase that involved 25 patients with CAP, 25 patients with NPLRTI, and 50 control subjects in whom nine, 13, and three, respectively, were positive for at least one of the RVs. The sample size was calculated on the basis of these data to detect a difference among the three groups in the proportions of participants positive for at least one of the RVs, with an α level of 0.05 and a power of 80% using standard methods. According to those calculations, the study required at least 162 participants in

each of the two patients groups. As a safety measure for the possibility of a lower rate of viral activity during the study period, we decided to significantly increase the size of the three study groups.

Data were recorded and analyzed using Epi Info version 3.3.2 software (Centers for Disease Control and Prevention; Atlanta, GA). Proportions between groups were compared using the χ^2 test, with Yates correction or Fisher exact test used as appropriate. Continuous variables were compared using analysis of variance when the Bartlett test showed the variance in the samples to be homogeneous and the Kruskal-Wallis test when the variance in the samples was shown to differ. Statistical significance was set at $P < .05$ throughout.

RESULTS

Three hundred and eighty-four hospitalized patients were recruited into the study on 165 random-sampling days over the course of 10 study months. Based on the radiologic criteria detailed in the "Materials and Methods" section, 183 patients were allocated to the CAP group and 201 to the NPLRTI group. Over the same time, 450 control subjects were recruited into the study. Table 1 presents a comparison of participant characteristics, including age, sex, smoking status, and vaccinations for the three study groups.

For data analysis purposes, any participant in whom at least one of the three samples was positive for one of the RVs was considered to be positive for that virus. Table 2 presents the distribution of the 12 viruses identified in the three study groups (individually and by virus group) together with a comparison of the frequency of each main virus group, the total number of viruses, and the total number of subjects showing positive for the viruses between the CAP group and the other two study groups. The number of viruses identified and the number of subjects showing positive for the viruses was significantly higher in the CAP group than in the control group and significantly lower than in the NLPRTI group. The same relationship was seen for influenza viruses and rhinovirus in the three groups. In the other two virus groups, RSV and coronaviruses, there were higher proportions in the CAP group compared with the control and NPLRTI groups.

The mean age of the 58 patients with CAP who were positive for at least one virus was 63.4 ± 17.5 years compared with 58.0 ± 21.6 years for the 125 patients with CAP in whom no virus was identified. This difference did not reach statistical significance. Fourteen (24%) of the patients with CAP with at least one virus were present or past smokers compared with 53 (42%) of those who were negative for all viruses ($P = .03$).

DISCUSSION

The present study is original and unique in two methodologic aspects. The first is the inclusion of two

control groups, one of which consisted of subjects without evidence of respiratory infection, who were sampled and tested together with the patients with CAP. Five studies have been reported over the past 4 years that investigated the proportion of viral respiratory infections in adult patients with CAP using NAAT.²⁻⁶ None of those studies included a control group of subjects without evidence of respiratory infection. The authors of each study cited a lack of this type of control group as a significant limitation of their study. A valid comparison with a healthy control group is necessary to assess the significance of the proportion of RV among patients with CAP. Another comparison group that was included in our study was patients hospitalized with NPLRTI. The reason for including this group was that, based on our previous studies,^{12,13} we expected the proportion of viruses in these patients to be significantly higher than in patients with CAP, an assumption that was confirmed in the present study.

The second original and unique aspect of this study is the collection of samples for viral testing by three different sampling methods. In five recent studies, patients with CAP were sampled by NPS,^{3,4} OPS,⁶ a combination of these two methods,² and a combination of OPS and throat washings.⁵ None of these studies tested or related the effect of the sampling method on the results of the study, even though some of them sampled the oropharynx exclusively and others the nasopharynx exclusively. In our recent study,¹¹ in which the present study population constituted the majority of that population, we found that the sampling method has a significant effect on the proportions of RVs identified. NPW yielded significantly higher proportions than OPS and NPS, but only the combination of all three sampling methods identified all the RVs. In light of this finding, it is reasonable to assume that the combination of three sampling methods, including NPW that was not used in the previous studies, had a significant effect on the increased proportion of RV identified in the present study.

The overall proportion of viruses identified and the proportion of patients with at least one identified virus were, as expected, significantly higher in the patients with CAP than in the control groups. However, the identification of 32 RVs in 7.1% of the control subjects is an important finding. In light of this finding, it is reasonable to assume that only in approximately 25% of patients with CAP (the difference between 31.7% and 7.1%) can a significant involvement of RVs in the disease process be claimed. This interpretation of the results also holds for each of the specific viruses that were identified with varying differences between patients with CAP and control subjects. The overall proportion of viruses among patients with NPLRTI,

Table 1—A Comparison of Participant Characteristics by Study Group

Characteristic	CAP (n = 183)	Controls (n = 450)	NPLRTI (n = 201)	P Value ^a
Male sex	105 (57)	207 (46)	92 (46)	.024
Age, y				
Mean ± SD	59.5 ± 20.6	62.2 ± 15.6	66.3 ± 18.5	< .01
Range	19-96	19-93	19-99	...
> 65	94 (51)	238 (53)	130 (65)	.01
Smoking status				
Former smoker	28 (15)	64 (14)	31 (15)	.897
Current smoker	40 (22)	61 (14)	30 (15)	.03
Former and/or current smoker	68 (37)	125 (28)	61 (30)	.067
Vaccination status				
Prior influenza vaccination	58 (32)	164 (36)	73 (36)	.499
Prior pneumococcal vaccination	14 (8)	80 (18)	23 (11)	< .01

Data are presented as No. (%), unless otherwise indicated. CAP = community-acquired pneumonia; NPLRTI = nonpneumonic lower respiratory tract infection.

^aThree-group comparison.

which was significantly higher than among patients with CAP, could be attributed mainly to influenza viruses that were identified in 31.3% of patients with NPLRTI. On this issue, it is noteworthy that our study population included patients with lower respiratory tract infection (LRTI) in whom we looked for viral etiologies. Thus, a patient with a clinical picture of LRTI diagnosed as influenza virus based on polymerase chain reaction findings was considered by us to be a patient with LRTI with an influenza etiology.

At least one RV in 31.7% of the patients with CAP is higher than the proportions of 15%, 21%, 23%, and 29% reported in four of the five studies cited previously.^{2-4,6} The higher proportion in our study can be attributed, for the most part, to the combination of

sampling methods that was used. The proportion in the present study is significantly lower than the outlying proportion of 56% that was reported in the fifth study⁵ but has not been confirmed in other studies. The frequency distribution of specific viruses is substantially different among these five studies. A grouping of the proportions of the principal viruses identified in these studies yields the following ranges: 4% to 12% for influenza viruses, 1% to 17% for rhinovirus, 2% to 13% for coronaviruses, 1% to 4% for RSV, 0% to 4% for human metapneumovirus, 0% to 4% for adenovirus, and 1% to 7% for parainfluenza viruses. The corresponding proportions from our study are within these ranges, except for RSV for which our proportion was higher than in previous studies.

Table 2—Frequency Distribution of the 12 Viruses Identified in the Three Study Groups^a

Virus	CAP (n = 183)	Controls (n = 450)	NPLRTI (n = 201)	P Value, CAP vs Controls	P Value, CAP vs NPRTLI
Coronaviruses	24 (13.1)	17 (3.8)	21 (10.4)	< .01	.513
NL63	3 (1.6)	6 (1.3)	2 (1.0)
229E	5 (2.7)	2 (0.4)	4 (2.0)
OC43	13 (7.1)	8 (1.8)	14 (7.0)
HKU	3 (1.6)	1 (0.2)	1 (0.5)
Respiratory syncytial virus	13 (7.1)	4 (0.9)	7 (3.5)	< .01	.172
Rhinovirus	9 (4.9)	9 (2.0)	15 (7.5)	.080	.413
Influenza viruses	8 (4.4)	2 (0.4)	63 (31.3)	< .01	< .01
Influenza A	8 (4.4)	2 (0.4)	62 (30.8)
Influenza B	0	0	1 (0.5)
Adenovirus	3 (1.6)	0	0
Human metapneumovirus	2 (1.1)	0	0
Parainfluenza 3 virus	0	0	3 (1.5)
Parainfluenza 2 virus	0	0	0
Total					
Viruses	59 (32.2)	32 (7.1)	110 (54.7)	< .01	< .01
Positive subjects ^b	58 (31.7)	32 (7.1)	104 (51.7)	< .01	< .01

Data are presented separately and by the principal virus groups and a comparison of the prevalence of the principal virus groups, all viruses, and all subjects showing positive for viruses between patients with CAP and the other two study groups. All values are presented as No. (%). See Table 1 legend for expansion of abbreviations.

^aThe percentage of subjects showing positive for the specific virus of all the subjects in the population.

^bPatients positive for at least one virus.

RV appears as one of the most common etiologies of CAP in the 2007 Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of CAP in adults.¹⁴ The specific viruses in that list include those detailed previously in this article, except for coronaviruses, rhinovirus, and human metapneumovirus. These three viruses are absent from the list because their involvement and importance in CAP⁹ only has been recognized in recent years with the expanded use of NAAT. Falsey et al¹⁵ in 2002 and van Elden et al¹⁶ in 2004 were the first to identify rhinovirus and coronaviruses in nonimmunocompromised adults with CAP. The proportion of 18% for this combination of viruses seen in our study is higher than the corresponding proportions of 4%, 7%, 9%, and 15% found in four of the five studies cited previously^{2-4,6} and significantly lower than the outlying proportion of 30% found in the fifth study.⁵ These high-prevalence proportions strongly highlight the need for the development of safe and effective antiviral agents for these two viruses, a need that also was cited in previous publications.¹⁷⁻¹⁹

The main limitation of the present study is that it has no real clinical correlation associated with it. In contrast to previous studies, this study ignored nonviral etiologies for CAP, which raises the question about whether the virus identified in the patients with CAP was the sole etiology for CAP or whether bacterial and atypical etiologies could have been identified as well in these patients and may have caused the clinical presentation and course of the disease. Because we did not evaluate bacterial and atypical etiologies, we cannot relate to possible associations between the RV identified in individual patients and the clinical course and outcome of CAP.

An additional methodologic limitation in the study is that the subjects were recruited over two winter periods and not continuously over all the seasons of the year. It is possible that this limitation of our study affected the results and should be taken into consideration when comparing them to those of the five studies described herein, all of which were conducted continuously over all seasons of the year. Another methodologic limitation is the exclusive use of NAAT without regard for other traditional methods, including serology, viral cultures, and immunofluorescence. Although each of those methods is less sensitive than NAAT, it is possible that testing of our samples by other methods would have increased the proportion of viruses identified in our study population. During the planning stage of the present study, we were well aware of these limitations. The inclusion of the two comparison groups made the study population much larger than similar studies in the past. Furthermore, the decision to use three sampling methods increased

the number of samples tested threefold. Given this magnitude of patients and samples, the study could only be conducted within the limitations discussed here.

In conclusion, the proportion of RV involved in CAP is higher than previously reported. The proportion of RV identified in healthy subjects is significantly lower than in patients with CAP, but it is not zero and should be considered when interpreting corresponding proportions among patients.

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Dr Shimoni: contributed to the participant sampling.

Dr Shemer-Avni: contributed to the study design and virologic tests.

Dr Keren-Naos: contributed to the virologic tests.

Dr Shtainberg: contributed to the virologic tests.

Dr Devora Lieberman: contributed to the study design, participant sampling, data analysis, and manuscript preparation.

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