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A comparative study of the etiology of adult upper and lower respiratory tract infections in the community

David Lieberman[a,b,*], Devora Lieberman[b], Igor Korsonsky[b], Miriam Ben-Yaakov[c], Zilia Lazarovich[c], Maureen G. Friedman[d], Bella Dvoskin[d], Maija Leinonen[e], Bella Ohana[f], Ida Boldur[c]

[a]*Pulmonary Unit, Soroka Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[b]*Division of Internal Medicine, Soroka Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[c]*The Microbiology Laboratory, Asaf Harofeh Hospital, Zerifin, Bar-Ilan University, Ramat-Gan, Israel*
[d]*Department of Virology, the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[e]*The National Public Health Institute, Oulu, Finland*
[f]*Savyon Diagnostics Ltd., Ashdod, Israel*

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Abstract

Lower respiratory tract infection and upper respiratory tract infection (URTI) are very common, but the etiology is not diagnosed in routine practice. The objective of this study was to determine and compare the frequency distribution of the various infectious etiologies for these diseases. One hundred seventy five adults in the community with febrile LRTI and 75 with febrile URTI were included in a purely serologically based prospective study. Paired sera were obtained for each of the patients and were tested by EIA or immunofluorescence methods to identify 14 different pathogens. Only a significant change in antibody titers between the paired sera was considered diagnostic. At least one infectious etiology was identified in 167 patients (67%). In the LRTI group, infection with at least one of 7 respiratory viruses was found in 88 patients (50%). One of the atypical pathogens was found in 40 patients (23%), of these *Legionella* spp. in 19 (11%) and *Mycoplasma pneumoniae* in 18 (10%). A bacterial etiology was found in 19 patients (11%), of these *Streptococcus pneumoniae* in 8 (5%) and β-hemolytic streptococci group A in 5 (3%). The frequency distribution of etiologies in the URTI group was not significantly different from the LRTI group, except for *M. pneumoniae* that was identified in only one patient with URTI ($p = 0.015$). More than one etiologic agent was found in 42 (17%) of the patients. LRTI is caused by a broad spectrum of etiologies, with respiratory viruses predominating and a moderate, but significant, prevalence of atypical pathogens. The frequency distribution of etiologies for URTI is similar to LRTI. In a significant proportion of patients with URTI and LRTI there is serologic evidence of infection with more than one pathogen. The justification and benefit of distinguishing between URTI and LRTI in routine clinical work is doubtful. When a decision is reached to treat RTI patients with an antibiotic, it is logical to use a macrolide or tetracycline.

Keywords: Etiology; Adults; Respiratory tract infection; Community; LRTI; URTI

1. Introduction

Respiratory tract infections (RTI) are very common in the community and are one of the major reasons for appointments to primary care physicians, particularly in the winter season (Macfarlane et al., 1993). The broad diagnosis of RTI includes the two principal sub-diagnoses of lower respiratory tract infection (LRTI) and upper respiratory tract infection (URTI), although it is often difficult to distinguish between them. The vast majority of RTI cases run a benign course, so it is not justified in routine practice to invest effort and means to identify the precise etiology. Primary care physicians who are called upon to reach management decisions for RTI patients should base these decisions, among other factors, on the known frequency distribution of etiologies for this type of infection. Data in the literature on these etiologies (Billas, 1990; Gleckman, 1987; Macfarlane et al., 1993; Monto & Cavallaro, 1971; Verheij et al., 1989) are based primarily on studies that did not utilize advanced diagnostic techniques that have been developed recently.

* Corresponding author. Tel.: +972-8-6400411; fax: +972-8-6403022.
E-mail address: lieberma@bgumail.bgu.ac.il (D Lieberman).

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The aim of the present study was to use innovative new serologic methods to identify the various infectious etiologies for febrile RTI among adults in the community. In light of the accepted division between LRTI and URTI, an additional aim of this study was to compare the frequency distribution of the infectious etiologies between these two sub-groups.

2. Materials and methods

2.1. Patients

The study included patients who went to their primary care physician or to the emergency room during the course of three months between January 1, 1999 and March 31, 1999, who met the inclusion criteria for the study and who agreed to participate in the study. Inclusion criteria were: (1) age above 21 years; (2) an acute febrile illness of less than one week's duration [by patient's report of at least one temperature measurement at home, or at the neighborhood clinic, or at the emergency room reaching at least 37.8°C (PO)]; 3) the patient had at least one of the following four complaints: cough, coryza, sore throat or hoarseness. Women who might be, or were definitely pregnant were excluded as were patients known to be positive for HIV.

Three primary care clinics of Klalit Health Services (the largest sick fund in Israel), in three different neighborhoods in the southern Israel city of Beer-Sheva, participated in the study. All board certified specialists in family medicine who work in those clinics participated in the study. A second source of patient enrollment was the emergency room of the Soroka Medical Center. Patients were enrolled in the study from this source on the condition that they met the inclusion criteria and were discharged shortly after they turned to the emergency room without being hospitalized. The study was approved by the Committee for Research on Human Beings (Helsinki Committee) of the Soroka Medical Center, and all participants gave informed consent.

2.2. Study protocol

Patients who were identified as meeting the study inclusion criteria and gave informed consent, were interviewed by the family physician or the emergency room physician using a detailed structured questionnaire. The physical examination focused on the patient's complaints and findings associated with respiratory tract infections. Throat cultures were taken from all patients by a research assistant who also drew 5 mL of venous blood for serologic tests. Shortly afterwards the blood samples were separated and the serum was frozen at –20°C until the serologic tests were performed. Each of the patients underwent a chest x-ray (P-A and lateral). Treatment decisions were reached by the treating physicians, without intervention by the study team. Telephone follow-ups of symptoms were conducted by a follow-up team at 48–72 h intervals. The follow-up focused on questions about the continuation of fever, the appearance of new symptoms and the continued presence or disappearance of the respiratory tract symptoms. The telephone follow-up continued until the patient was free of complaints and gradually returned to his/her usual schedule of activity. Three to four weeks after entering the study the patients were invited for a follow-up visit. At this meeting a second blood sample was drawn from each patient for convalescence phase serology. Patients with a positive throat culture or suspected pneumonia in the acute phase of their illness also underwent repeat throat cultures or chest x-rays, accordingly. Pneumonia was diagnosed only in patients with a suspected lung infiltrate that disappeared or cleared significantly in the follow-up x-ray.

2.3. Classification of LTRI and URTI

At the data analysis stage patients were divided into an LRTI group and a URTI group. For this purpose we adopted Macfarlane's definition of LRTI (Macfarlane, 1999), according to which LRTI is diagnosed in the presence of a cough and at least one of: purulent sputum, dyspnea, chest pain or discomfort, wheezing and/or new focal crepitations or reduced breath sounds on lung auscultation. All enrolled patients who did not meet the diagnostic criteria for LRTI were defined as URTI.

2.4. Etiologic diagnoses

The etiologic work-up in this study was based, almost exclusively, on serologic tests. The only exception to this rule was group A β-hemolytic streptococci, which was diagnosed in the presence of a positive standard throat culture for this bacterium, taken in the acute phase of the illness, and on the condition that the follow-up throat culture in the convalescence phase was negative. Serologic tests were conducted for 14 pathogens known to cause upper or lower RTI, which can be identified in serologic tests. In all serologic tests, the two serum samples were tested in the same run for each of the patients. The methods, kits and criteria used to reach serologic diagnoses were as follows:

The antibody level for *Mycoplasma pneumoniae* was determined by a commercial enzyme immunoassay (EIA) kit SeroMp™ (Savyon Diagnostics, Israel). In this kit antibody levels for specific IgM, IgG and IgA antibodies are determined separately. *M. pneumoniae* was considered to be the etiology of the RTI if a significant change (according to the formula in the manufacturer's instructions) in the antibody level was found between the acute and convalescence serum samples.

Serologic testing for *Coxiella burnetii* was performed using the indirect immunofluorescence method. Antigen-coated slides (Biologic Institute, Nes-Ziona, Israel) were used with the *C. burnetii* strain QNM serving as the antigen. *C. burnetii* was considered to be the etiology of the RTI in

the presence of a fourfold or greater change in anti-*C. burnetii* phase II IgG and/or IgM antibody titers between the paired serum samples.

Antibodies to 41 different serogroups of *Legionella* spp. were detected using the indirect immunofluorescence method. Heat-killed *Legionellae* served as antigen (in 17 pools). All sera were tested for IgM after treatment with goat antibody to human IgG antibody. *Legionella* spp. were considered to be the etiologic cause of the RTI when a fourfold or greater increase in IgG and/or IgM titers between the paired serum samples was detected.

Chlamydophila (Chlamydia) pneumoniae-specific serum IgG, IgA and IgM levels were determined by the microimmunofluorescence (MIF) method using a commercial kit (SeroFIA-Chlamydia, Savyon Diagnostics, Ashdod, Israel). Elementary bodies of *C. pneumoniae* (Washington Research Foundation, USA) were used as antigen. All sera were tested for IgM after treatment with goat antibody to human IgG antibody. Sera were tested for the three antibody classes in serial twofold dilutions from 1:8 to the end-point. *C. pneumoniae* was considered to be the etiology of the RTI in the presence of a fourfold change in one or more of the three antibody classes between paired serum samples.

Antibody levels for seven respiratory viruses (influenza A, influenza B, parainfluenza 1, 2 and 3, respiratory syncytial virus and adenovirus) were determined by EIA using specific commercial kits for detection of IgG, IgA and IgM for all seven viruses (Genzyme Virotec, Germany). Infection with any of the seven viruses was considered to be the etiology of the RTI if a significant change of more than 5 Virotec units (adjusted OD) in the antibody level was found between the first and second serum samples. For patients who were immunized for influenza during the six months prior to their present illness, only an increase in antibody titer between the two sera was considered diagnostic of acute infection with influenza A or B. A decrease in antibody titer for these viruses was attributed to the effect of immunization.

IgG antibody levels to pneumococcal protein toxin, pneumolysin, produced in *Bacillus subtilis*, and to C-polysaccharide, isolated from a pneumococcal mutant strain with C-polysaccharide capsule (C-mutant CSR, SCS-2, clone 1) by the method of Pedersen et al. (Pedersen et al., 1982), were measured by enzyme immunoassay (EIA). A twofold or greater increase in antibody level between paired sera was considered diagnostic for *Streptococcus pneumoniae* infection (Jalonen et al., 1989; Jalonen et al., 1990). *S. pneumoniae*-specific immune complexes were determined by measuring antibody levels to pneumolysin and C-polysaccharides from precipitated and redissolved immune complexes (Holloway et al., 1993; Leinonen et al., 1990). The cut-off value for positivity was derived from results obtained by testing immune complex bound antibodies from 40 healthy adults (mean ± 2SD). Thus, the etiologic diagnosis of current pneumococcal infection as a cause of RTI was based on the presence of a significant change in the level of pneumococcal antibodies or the presence of specific immune complexes in any serum.

Table 1
A comparison of demographic data, smoking and chronic co-morbidity between URTI (n = 75) and LRTI (n = 175) patients

Variable	URTI	LRTI	p
Age (years; mean ± SD)	35.0 (13.3)	41.5 (15.4)	0.002
Males [n (%)]	38 (51)	79 (45)	NS
Current smoker [n (%)]	16 (21)	45 (26)	NS
Chronic co-morbidity [n (%)]			
Obstructive lung disease	1 (1)	19 (11)	0.02
Diabetes mellitus	1 (1)	5 (3)	NS
Coronary heart disease	2 (3)	11 (6)	NS
Hypertension	2 (3)	20 (11)	0.03
None	70 (93)	129 (74)	0.001

Total antibody levels to non-encapsulated *Hemophilus influenzae* (Burman et al., 1994) and *Moraxella catarrhalis* (Claesson & Leinonen, 1994; Leinonen et al., 1981) were measured by EIA using whole bacterial cells as antigens. A threefold increase or more in antibody levels between paired sera was considered diagnostic for current *H. influenzae* or *M. catarrhalis* infection as the etiology of RTI. Serologic tests for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* were conducted at the National Public Health Institute Department in Oulu, Finland.

2.5. Data analysis

The results were analyzed using the statistical software Epi Info. The χ^2 test or its equivalent served to compare proportions between groups and analysis of variance (ANOVA) was done to compare continuous variables among two or more groups. Statistical significance was set at $p < 0.05$.

3. Results

Two hundred fifty patients comprised the study population. One hundred fifty patients (60%) were enrolled into the study from the primary care setting and 100 others (40%) from the emergency room. In accordance with the classification described above 175 patients (70%) were diagnosed as LRTI and 75 (30%) as URTI. Table 1 presents a comparison of demographic data, smoking history and chronic co-morbidity between the two groups. All 250 patients, without exception, came to the follow-up appointment. A convalescence serum sample was drawn from all the patients at a mean interval of 26.2 ± 7.1 days (range 19–47 days) after the acute phase sample. The disease course in all 250 patients was benign and all recovered completely without significant complications or need for hospitalization.

Table 2 shows a comparison of the clinical manifestations of acute respiratory tract infection in the two groups.

Table 2
A comparison of signs and symptoms of RTI between URTI (n = 75) and LRTI (n = 175) patients

Variable	URTI	LRTI	P
Maximum temperature (°C; mean ± SD)	38.8 (0.7)	38.8 (0.7)	NS
Days with fever (mean ± SD)	3.9 (2.0)	4.4 (2.0)	NS
Chills [n (%)]	59 (79)	111 (63)	0.02
Sudden onset of disease [n (%)]	23 (31)	91 (52)	0.003
*Cough [n (%)]			
Any cough	39 (52)	175 (100)	
Dry	39 (52)	44 (25)	
White or translucent sputum	0 (0)	43 (25)	
Purulent sputum	0 (0)	80 (46)	
Bloody sputum	0 (0)	8 (5)	
Coryza [n (%)]	39 (52)	125 (71)	0.005
Sore throat [n (%)]	55 (73)	84 (48)	0.0004
Hoarseness [n (%)]	14 (19)	51 (29)	NS
*Dyspnea [n (%)]	8 (11)	83 (47)	
Weakness/fatigue [n (%)]	73 (97)	169 (97)	NS
Arthralgia/myalgia [n (%)]	59 (79)	143 (82)	NS
Headache [n (%)]	68 (91)	152 (87)	NS
Earache [n (%)]	18 (24)	52 (30)	NS
*Chest pain/discomfort [n (%)]	2 (3)	21 (12)	
Pharyngeal erythema [n (%)]	67 (89)	122 (70)	0.002
Enlarged tonsils [n (%)]	42 (56)	37 (21)	<0.000001
Tonsillar exudate [n (%)]	25 (33)	13 (7)	<0.000001
Sinus tenderness on palpation [n (%)]	10 (13)	29 (17)	NS
Tender cervical lymph nodes [n (%)]	28 (37)	31 (18)	0.002
*Localized reduction in breath sounds [n (%)]	0 (0)	11 (6)	
*Wheezing on auscultation [n (%)]	0 (0)	35 (20)	
*Crepitations on auscultation [n (%)]	0 (0)	45 (26)	

* Included in definition of LRTI, so comparison between groups is meaningless.

No comparisons were done for the clinical parameters that served as diagnostic criteria for LRTI, as such a comparison would be meaningless.

Table 3 presents the frequency distribution of the various infectious etiologies that were identified in each of the two groups, and a comparison between them. At least one infectious etiology was identified in 167 patients (67%), of whom 115 (66%) were in the LRTI group and 52 (69%) were in the URTI group. As can be seen in this table, the only statistically significant difference between the groups was for *Mycoplasma pneumoniae*. The relatively low rate of *C. pneumoniae* infections stems from the diagnostic requirement of a fourfold increase in antibody titer between the acute and convalescence phase sera, that was also used for other pathogens. Had we related to a high antibody titer, without change between the paired sera, as evidence of acute infection with *C. pneumoniae*, we would have identified this pathogen in 28 patients (16%) in the LRTI group and in 14 patients (19%) in the URTI group. In 11 of the 12 patients in whom pneumococcal infection was diagnosed a significant change in the level of pneumococcal antibodies was detected, while in only one patient the diagnosis was based only on the presence of specific pneumococcal immune complexes in the two sera.

Table 3
A comparison of the frequency distribution of infectious etiologies between URTI (n = 75) and LRTI (n = 175) patients

Pathogen	URTI	LRTI	p
Viral agents [n (%)]			
influenza virus type A	16 (21)	35 (20)	NS
influenza virus type B	16 (21)	26 (15)	NS
parainfluenza virus type 1	1 (1)	4 (2)	NS
parainfluenza virus type 2	2 (3)	4 (2)	NS
parainfluenza virus type 3	1 (1)	2 (1)	NS
adenovirus	1 (1)	11 (6)	NS
respiratory syncytial virus	1 (1)	10 (6)	NS
one of more of the above	37 (49)	88 (50)	NS
Bacterial agents [n (%)]			
S. pneumoniae	4 (5)	8 (5)	NS
H. influenzae	1 (1)	5 (3)	NS
M. catarrhalis	0 (0)	1 (1)	NS
Beta-hemolytic streptococcus	6 (8)	5 (3)	NS
one or more of the above	11 (15)	19 (11)	NS
Atypical bacterial agents [n (%)]			
Legionella spp.	9 (12)	19 (11)	NS
M. pneumoniae	1 (1)	18 (10)	0.015
C. burnetii	1 (1)	3 (2)	NS
C. pneumoniae	0 (0)	2 (1)	NS
one or more of the above	11 (15)	40 (23)	NS
Unknown agent	23 (31)	60 (34)	NS

The 28 patients in whom at least one of the *Legionella* spp. was identified as the etiology of RTI are a unique and interesting group. In light of this uniqueness it would be worthwhile to detail the specific *Legionella* spp. that were identified, the clinical manifestations of the infection, and the response to antibiotic therapy in these patients compared to the others. However, this degree of detail would be beyond the scope of the present paper that deals with all the infectious etiologies found in the study population. Thus, these patients were described and discussed in detail in a paper devoted specifically to this issue (Lieberman et al., 2001).

In 42 patients more than one etiology was identified. This represents 17% of the study population and 25% of the patients in whom at least one etiology was found. The distribution of etiologies per patient in the two groups, and the comparison between them, are shown in Table 4. Despite the absence of a statistically significant difference in the rates of this parameter between the two groups, there is a clear trend to a higher rate of more than one etiology in the LRTI group compared to the URTI group. Among these 42 patients, 10 had a viral respiratory tract infection in addition to a bacterial agent, 23 patients had a viral respiratory tract infection together with an atypical bacterial agent, and four

Table 4
A comparison of the number of infectious etiologies per patient between URTI (n = 75) and LRTI (n = 175) patients

Number of etiologies	URTI	LRTI	p
0	23 (31)	60 (34)	NS
1	44 (59)	81 (46)	NS
2	8 (11)	30 (17)	NS
3	0 (0)	4 (2)	NS

patients had a combined infection with a bacterial and an atypical bacterial agent. Three pathogens were identified in one patient, each agent belonging to one of the above groups. Four patients had infections with more than one agent from the same group of pathogens.

Nineteen patients from the LRTI group (11%) were diagnosed with community-acquired pneumonia (CAP). In 14 of these patients at least one infectious agent was identified. Two patients had a mixed etiology with a respiratory virus and an atypical bacteria, one patient had a combination of a viral agent, *C. pneumoniae* and *S. pneumoniae* and one patient had a mixed infection with a viral agent, *C. burnetii* and a positive throat culture for group A β-hemolytic streptococci.

4. Discussion

The frequency distribution of the etiologies of RTI in adult patients in the community was determined in a previous study (Lieberman et al., 1998) that we conducted two years ago as a pilot study for the present one. Because of the small sample size in that study and the difficulty in distinguishing on clinical grounds between LRTI and URTI, the two sub-groups were united under the title of RTI. The lessons learned from that study and from other studies using the same methodology had particular bearing on the serologic criteria for diagnosis of acute infection in the broad range of respiratory pathogens tested. Using accepted serologic criteria in the previous study we considered high antibody titers (particularly IgM or IgA, but in the case of *C. pneumoniae* IgG as well), which were unchanged between the paired sera, as evidence of acute infection with the specific agent. This diagnostic approach increased the sensitivity of the tests but reduced their specificity. We could not be certain using these criteria that all identified cases represented actual acute infections and not persistently high antibody titers resulting from a previous infection or an expression of chronic infection with a specific pathogen. Thus, in the present study we diagnosed acute infection only in the presence of a significant increase in the antibody titer or level between the paired sera in one of the specific immunoglobulins. This strategy increased our confidence that the identified pathogen was indeed the etiologic cause of the RTI, but at the same time it reduced the sensitivity of the tests and is responsible, at least in part, for our finding that in one third of the patients the infectious agent is unknown.

The etiologic diagnoses in our study were based almost entirely on serologic response between paired sera for a very broad range of respiratory pathogens. We were very aware of the theoretical possibility that the antibody response upon which the diagnoses were based could be non-specific, despite our efforts to reduce this problem to a minimum, as discussed above. However, we preferred serologic testing to isolation of pathogens from respiratory secretions. The microbial culture methods may have a very low sensitivity for some pathogens, and even when a potential pathogen is isolated from secretions there is no way of proving that its presence is not due to contamination unrelated to the disease, especially in the case of pneumococcus, *H. influenzae*, and *M. catarrhalis*, which belong to the normal microbial flora of the upper respiratory tract. In contrast, a significant change in antibody titer for a specific pathogen between the paired sera usually indicates a significant association between the pathogen and the host with a high level of probability for a cause-effect relationship between the pathogen and the disease.

Among the inclusion criteria in our study was the mandatory requirement for fever, measured before or at the time the patient visited the physician. As a result of this requirement only cases of febrile RTI were included, although without doubt many cases of RTI do not involve fever. The grounds for this decision was our desire to exclude patients who met the inclusion criteria but whose complaints resulted from an allergic cough or coryza and not from acute infection. The requirement of fever effectively prevented, in our opinion, the inclusion of these patients in the study.

In order to compare the frequency distribution of the different infectious etiologies between the LRTI and the URTI groups, we had to define LRTI. A comprehensive survey of the definitions of LRTI or acute bronchitis used by investigators in 22 different studies showed that the number of definitions is similar to the number of studies (Macfarlane, 1999). Among all the definitions that have been proposed we chose to use Macfarlane's definition (Macfarlane, 1999), which despite the problems involved in its application, seemed to be the most logical. Our use of this definition of LRTI brought about a situation in which many patients who had both URTI and LRTI symptoms were defined as LRTI. This situation should be taken into account in interpreting the results of our study.

In a comprehensive search of the literature only one study of the broad range of etiologies of LRTI among adults in the community was found (Macfarlane et al., 1993). In that study pneumococcus was the dominant etiology with an almost non-existent prevalence of atypical pathogens. The population in that study was significantly older and had a higher rate of chronic co-morbidity, particularly chronic respiratory problems, than our population. The pneumococcal etiology was diagnosed in that study by the presence of the bacterium or its antigen in sputum, in contrast to the

present study in which we purposely avoided this approach, as discussed above. The spectrum of etiologies that was tested in that study did not include most of the *Legionella* spp. and the diagnostic methods for viruses and atypical pathogens were much less sensitive than those used in the present study. The methodological differences between these studies provide an explanation for the striking difference between the etiologic distributions found in the two studies. The frequency distribution for LRTI found in our study points to a clear dominance of viral etiologies, significant rates of atypical pathogen etiologies particularly *M. pneumoniae,* and various *Legionella* spp. and only a small portion of the classic bacterial etiologies. The distribution found in our study is closer to that appearing in the literature, namely that "acute bronchitis is caused frequently by viruses, less commonly by *M. pneumoniae* and rarely by bacterial pathogens, namely *Legionella* spp, and *Bordetella pertussis*" (Gleckman, 1987). We believe that the difference between the present study and these studies in the prevalence of *Legionella* spp. is due to the progress made over the past decade in serologic diagnostic techniques for the identification of these pathogens. This progress, which is manifested in the results of our study, were not available for studies that were conducted more than ten years ago.

Our findings in relation to several specific etiologies require further discussion. *C. pneumoniae* was identified in only two patients in the LRTI group. This percentage is low in both absolute and relative terms to the rate of infections with this pathogen reported in a previous study (Grayston et al., 1986). The reason for this low rate of *C. pneumoniae* infections in contrast to previous studies is that in our study we diagnosed acute infection with this pathogen only in the presence of a significant increase in antibody titer between the paired sera. This contrasts with earlier studies in which high antibody titers were considered diagnostic of acute infection even without change between paired sera. Today, high IgG and IgA titers for *C. pneumoniae* without change between acute and convalescence phase sera in COPD patients are viewed as evidence of chronic infection with this pathogen (von Hertzen et al., 1997). Thus, we decided that it would be wrong to diagnosis all patients in our study with high antibody titers as suffering from an acute infection with this pathogen. If we had used those parameters we would have identified 42 patients as serologically positive for *C. pneumoniae,* with 16% in the LRTI group and 19% in the URTI group. In addition to the high positivity rates in absolute terms, this method would not have demonstrated the sharp difference in rates of infection with this pathogen between LRTI and URTI, which have been reported in the past (Grayston et al., 1986).

In contrast to all other studies on the etiologies of LRTI that identified very low and even miniscule rates of infection with *Legionella* spp., we found 28 patients with this etiology, with a rate of positivity of 11% among LRTI patients and 12% among URTI patients. The principal reason for these differences between the present and previous studies is the number and type of specific serogroups included under the heading *Legionella* spp. In the vast majority of previous studies only *L. pneumophila* was identified, and in most cases only its serotype 1. This serogroup of *Legionella* causes severe illness in a large percentage of infected patients that involves the lung parenchyma and is responsible apparently for reports of CAP that necessitates hospitalization in intensive care units (Hirani & Macfarlane, 1997; Woodhead et al., 1986). In contrast, in the present study we tested 40 other serogroups of *Legionella* spp. in addition to serotype 1. Since a significant change in antibody titer was found in all 28 patients with *Legionella* spp. for at least one of these serogroups, it is reasonable to assume that there is a significant association between that serogroup and the RTI.

Three known respiratory tract bacteria, namely *S. pneumoniae, H. influenzae* and *M. catarrhalis,* were tested using innovative serologic techniques that are not in routine use. The prevalence rates of these bacteria in our study were very low. This finding contrasts strongly with the results of a previous study of ours that found a positive serologic rate of 42.8% for *S. pneumoniae* in hospitalized CAP patients (Lieberman et al., 1996). This striking difference in prevalence rates for *S. pneumoniae* between the two populations was found even though the tests were done in the same laboratory using the same methods. We believe that this difference provides evidence for the high level of reliability of the tests and indicates that although *S. pneumoniae* is a very common etiology among hospitalized CAP patients, its prevalence is very low among LRTI and URTI patients in the community.

An inevitable limitation of a study of this type is that the results may be specifically related to factors such as season of the year, age group, patient composition, and geographic area. Although the year in which the study was conducted was not atypical in frequency of viral infections and did not have an epidemic of *M. pneumoniae* infections, the three study months did include January and February with their regular seasonal peak of influenza A and B infections. On the basis of a previous epidemiologic study (Monto & Cavallaro, 1971) it is reasonable to assume that the distribution of etiologies in the pediatric age group, even in our region, is different from the results of the present study.

In a third of our patients there was no evidence of defined infectious etiology despite the intensive investigation of paired sera. We believe that there are two primary explanations for this finding. First, the criteria for specific etiologic diagnosis did not include an unchanged high antibody titer between the sera. This requirement, which is explained above, increased the diagnostic specificity but apparently reduced the sensitivity leading to the classification of unknown etiology in some of the patients. Second, there may be other viral etiologies, such as rhinovirus and coronavirus, which are known to cause acute bronchitis (Gleckman, 1987) but are technically difficult to diagnose. It is possible that some of the patients in our study were infected with

these viruses, although as a general rule these infections cause an afebrile illness (Gleckman, 1987) while all the patients in this study were febrile.

In one quarter of the patients in our study in whom an etiology was found, more than one pathogen was identified. The association of more than one infectious agent with the development of respiratory tract infection is well known (Verheij et al., 1989) and has been attributed in the past to bacterial infection that is secondary to viral infection. Two studies that used advanced serologic techniques to assess the etiology of CAP in hospitalized patients reported a high rate of 38% of patients with evidence of more than one etiology (Kauppinen et al., 1995; Lieberman et al., 1996). Those studies, like the present one, found all possible combinations of pathogens and not only an association between bacteria and viruses. Since RTI and CAP involve infection of the same system and have overlap features, it is likely that the pathophysiological explanations given for the phenomenon of multiple etiologies in CAP (Lieberman et al., 1996) are valid for RTI as well. Despite the absence of statistical significance (because of the small number of patients) there is a clear trend to increased rates of multiple etiologies in the LRTI group (19%) compared to the URTI group (11%). This difference, together with the rate of 38% of patients with more than one etiology in CAP, leads to the conclusion that this phenomenon increases in prevalence as the infection involves lower regions of the respiratory tract, i.e., lowest in URTI, higher in LRTI and highest in CAP. This phenomenon can be viewed from the opposite perspective, i.e., if more pathogens are involved in the infection, the infectious process involves lower regions of the respiratory system.

The division of RTI into URTI and LRTI is problematic in terms of the primary physician's daily clinical routine because of the overlap of many expressions of infection in these two parts of the respiratory tract. This overlap is particularly well demonstrated in Table 2, which presents a comparison of clinical manifestations between the two groups and shows that clinical signs that are characteristic of one type of infection also appear at relatively high rates in the other. The division of RTI is also not necessary on pathophysiological grounds, since the upper and lower respiratory tracts are continuous and the ciliary structure of the mucosa is identical in both. From the theoretical standpoint it is important to diagnose and treat all patients with CAP with antibiotics, but only those RTI patients without CAP who have pharyngitis or tonsillitis caused by group A β-hemolytic streptococci. Beyond these latter two diagnoses, there is no therapeutic significance to the differentiation between URTI and LRTI since in neither case is there clear cut justification for antibiotic therapy. Another aspect that might have provided justification for the division of RTI is the etiologic distribution. The important finding in our study in this respect is that there is no significant difference in the frequency distribution of infectious etiologies between URTI and LRTI, except for *M. pneumoniae*. The relevant question that should be posed is whether the higher rate of *M. pneumoniae* in respiratory tract infections that meet the criteria for LRTI justifies the differential diagnosis between URTI and LRTI. We believe that this question remains unanswered at the moment.

The therapeutic significance of our results is complex. The predominance of viral etiologies in both types of infection does not support antibiotic therapy. The significant moderate rate of atypical agents would appear to support antibiotic treatment, although at least in some of these patients the disease is self-limited and antibiotic therapy does not affect the outcome. Classic bacterial etiologies were identified in a low rate of patients in both RTI subgroups, but it is reasonable to assume that antibiotic therapy would have a favorable effect on outcome in these patients. The results of this study cannot contradict the conventional approach that antibiotic therapy is not indicated in RTI (Gleckman, 1987), or at least that its use is controversial (Billas, 1990). In any event the results of our study indicate that in RTI patients for whom the treating physician decides to prescribe antibiotics the choice should be a macrolide or tetracycline.

We conclude that LRTI is caused by a broad range of etiologic agents, with viral predominance and a moderate, but significant rate of atypical bacterial etiologies. The frequency distribution of etiologies of URTI is similar to LRTI. A significant percent of RTI patients have evidence of more that one etiologic agent. The need to distinguish between URTI and LRTI in routine primary care work is doubtful. If a decision is reached to treat RTI patients with antibiotics, the logical choice should be a macrolide or tetracycline.

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