

Infectious aetiologies in elderly patients hospitalised with non-pneumonic lower respiratory tract infection

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Abstract

Objective: to identify the infectious aetiologies of non-pneumonic lower respiratory tract infections in hospitalised elderly patients, and to characterise the patients in terms of demographic, clinical and therapeutic variables.

Design: a prospective, non-interventional, purely serologically based diagnostic study.

Setting: a tertiary university hospital in southern Israel.

Subjects: 133 elderly patients hospitalised for non-pneumonic lower respiratory tract infections.

Methods: paired sera were obtained for each of the hospitalisations and were tested using immunofluorescence or enzyme immunoassay methods to identify 13 different pathogens. Only significant changes in antibody titers or levels between the paired sera were considered diagnostic.

Results: at least one infectious aetiology was identified in 77 patients (58%). At least one of seven viral aetiologies was identified in 52 patients (39%). A bacterial aetiology was identified in 27 patients (20%) including *Streptococcus pneumoniae* in 24 (18%). An atypical bacterium was found in 27 patients (20%) including *Mycoplasma pneumoniae* in 15 (11%) and *Legionella* spp. in nine (7%). More than one aetiology was found in 23 patients (17%). One hundred and twenty nine patients (96%) suffered from serious chronic co-morbidity. One hundred and twenty one patients received antibiotics during their hospitalisation, 106 (80%) with a beta-lactam and 42 (31%) with another antibiotic.

Conclusions: non-pneumonic lower respiratory tract infection is caused in hospitalised elderly patients by a broad spectrum of aetiological agents, primarily respiratory viruses with a significant, though lesser, prevalence of classical and atypical bacteria. Despite this distribution of aetiologies, most patients are treated with beta-lactam antibiotics. The indication for antibiotic therapy in these patients and the choice of antibiotic preparation should be addressed in further studies.

Keywords: elderly, hospitalisation, respiratory, infection

Introduction

Lower respiratory tract infection (LRTI) is very common in all age groups, especially in winter, and is usually treated in the primary care setting. This diagnostic category includes two principal diagnoses that have a

different clinical and therapeutic significance. The more serious of the two is community-acquired pneumonia (CAP), which necessitates hospitalisation for a minority of younger patients and many elderly patients [1]. The second is non-pneumonic LRTI, which is much more common than CAP but has a much more benign clinical

course. Hospitalisation is rarely required for younger patients with this disease. However, non-pneumonic LRTI can cause a severe disease requiring hospitalisation in the elderly population. Although hospitalisation for this acute disease is not uncommon among elderly patients, we did not find a single article on this subject in a comprehensive literature search. Thus, the objective of this study was to identify the infectious aetiologies of non-pneumonic LRTI in hospitalised elderly patients, and to characterise the patients in terms of demographic, clinical and therapeutic variables.

Material and methods

Patients

All patients hospitalised for LRTI during the period between 1 November, 1998 and 15 March, 1999 in the internal medicine and intensive care wards of the Soroka Medical Center in Beer-Sheva Israel who met the inclusion criteria, and gave consent to participate, were included in the study. Only first hospitalisations were included for patients who had repeat hospitalisations during the study period. The study was approved by the Helsinki Committee for research on human beings of the Soroka University Medical Center, and all participants gave informed consent to participate.

Inclusion criteria for the study group were the fulfilment of all of the following five conditions: (1) age above 65 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 neighbourhood clinic, or at the emergency room reaching at least 37.8°C (PO)]; (3) a cough that began or worsened significantly during the week prior to hospitalisation; (4) in the week prior to hospitalisation at least one of the following complaints: (a) new appearance or worsening of shortness of breath, (b) sputum production, (c) wheeze, (d) chest pain or discomfort; and (5) absence of an infiltrate on anterior-posterior and lateral chest x-rays. Exclusion criteria were: (1) patients hospitalised from nursing homes; and (2) patients with documented COPD.

Study protocol

All patients were hospitalised by decision of the emergency room physicians, without intervention on the part of the investigators. Every 24–48 hours a research assistant visited each of the internal medicine and intensive care wards and identified patients hospitalised in the interim who met the inclusion criteria for the study. After the patient agreed to participate in the study he/she was interviewed concerning chronic diseases, smoking habits, and complaints and symptoms of their current acute disease. During the first meeting a blood sample of 5 ml was drawn for serological testing.

The blood sample was centrifuged shortly after being drawn and the serum was frozen at a temperature of -20°C until serological tests were conducted. The medical information received from patients or their accompanying party were corroborated and additional relevant medical, laboratory and administrative data were collected from the medical records. Decisions as to whether to give antibiotic therapy, its type, mode and duration of administration were reached by the treating physicians in the hospital wards, without intervention on the part of the investigators.

Upon discharge from the hospital the patient was invited to a follow-up appointment at the pulmonary clinic of the Soroka Medical Center, 3–5 weeks after admission to the hospital. At that clinic follow-up data were collected on the course of the convalescence and abnormal events that may have occurred following discharge from the hospital. Each of the patients had a second (convalescence phase) serum sample taken at this meeting for serological testing. This sample was handled in exactly the same manner as the previous acute phase sample.

Aetiologic diagnoses

The aetiological work-up in this study was based exclusively on serological testing. Serological tests were conducted to identify 13 pathogens known to be infectious agents in the upper and/or lower respiratory tract that can be diagnosed by serological methods. The paired sera for each patient were tested in the same run in all cases. The methods, kits and criteria have been described by us in detail in a previous publication [2].

Serological tests for seven respiratory viruses, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* were conducted using the enzyme immunoassay (EIA) method. MIF serology was used for identification of *Legionella* spp. and *Chlamydia* (*Chlamydia pneumoniae*). Only a significant change in the antibody level or titre for a specific pathogen between the acute and convalescence serum samples was considered diagnostic for infection with that pathogen, so only patients for whom paired sera were obtained were included in the final data analyses.

The criteria for a significant change between paired sera for each pathogen are listed below: *M. pneumoniae* was considered to be the cause of the non-pneumonic LRTI in accordance with the formula in the manufacturer's instructions; *C. pneumoniae* in the presence of a 4-fold or higher increase in the titer of one or more of the three antibody classes; and *Legionella* spp. when a 4-fold or greater increase in IgG and/or IgM titers was detected. For any of the seven viruses a change of more than 5 Virotec units (adjusted OD) in the antibody level was required. For current pneumococcal infection a 2-fold or greater increase was necessary, and a 3-fold increase or more was considered diagnostic for current *H. influenzae* or *M. catarrhalis* infection.

Data analysis

The results were analysed 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 $P < 0.05$.

Results

The study consisted of 144 elderly patients hospitalised for non-pneumonic LRTI during the study period who met the inclusion criteria and gave their informed consent to participate. Since the aetiological diagnoses in this study were based on changes in antibody titre between the acute phase serum and the convalescence serum, we did not include in the data analyses four patients who died during the course of their hospitalisation and four patients from whom convalescence serum was not obtained. Convalescence sera were obtained from the 136 patients at a mean of 28.0 ± 4.9 (mean \pm SD) days (range 21–39 days) after the first sample was drawn at admission to the hospital. Three additional patients were excluded from the data analyses because we found a polyclonal response to all of the pathogens tested. In all, 133 patients were included in the final data analysis.

Table 1 presents the age and gender distributions of the study population together with data on hospitalisation rates in the previous year, current and past smoking habits, and immunisation rates for influenza and pneumococcus. Chronic co-morbidity is shown in the Table by type of illness. At least one serious chronic disease was found in 96% of the patients. The decision to hospitalise patients stemmed, in most cases, from a

Table 1. Demographic data, smoking history, immunisation and chronic co-morbidity in the study population

Variable	All patients (n = 133)
Age (years)	
Mean \pm SD	75.0 \pm 6.6
Range	65–92
Gender	
Males (n (%))	67 (50)
Patients hospitalised in previous year (n (%))	46 (35)
Smoking (n (%))	
Ex-smokers	23 (17)
Current smokers	29 (22)
Immunised (n (%))	
Influenza	31 (23)
Pneumococcus	3 (2)
Chronic co-morbidity (n (%))	
Cardiovascular	87 (65)
Pulmonary disease	68 (51)
Diabetes mellitus	46 (35)
Other serious chronic disease	22 (16)
No serious chronic co-morbidity	5 (4)

loss of control of the chronic disease due to the non-pneumonic LRTI, or because of the presence of the chronic disease *per se*. In addition to the LRTI symptoms that served as inclusion criteria, 30 patients (23%) had classic symptoms of URTI such as running nose, and/or sore throat, and/or hoarseness. During the course of hospitalisation patients had temperatures above 37.8°C for a mean of 2.1 ± 1.1 days.

Table 2 details the frequency and types of antibiotic therapy prior to and during hospitalisation and recommendations for treatment after discharge from the hospital. The low rate of antibiotic therapy prior to hospitalisation is striking in comparison to the high percentage of patients who received antibiotics in the hospital, particularly beta-lactam agents, most by the i.v. route.

Table 3 presents the frequency distribution of the various infectious aetiologies identified for the 133 patients in accordance with the results of serological testing for the 13 respiratory pathogens. In 77 patients (58%) at least one infectious aetiology was identified, while in the other 56 (42%) no infectious aetiology was diagnosed. In 52 patients (39%) at least one of the seven respiratory viruses was found. In 27 patients (20%) at least one of the three bacteria was identified: *S. pneumoniae*, *H. influenzae* or *M. catarrhalis*. In 27 patients (20%) at least one of the following three atypical bacteria was identified: *M. pneumoniae*, *Legionella* spp. and *C. pneumoniae*. In the nine patients in whom *Legionella* spp. was found, the distribution of serogroups was: *L. pneumophila* 1 in none, *L. pneumophila* other than 1 in 6, and *Legionella non-pneumophila* in three patients. In 54 patients (41%) a single aetiology was identified, while in 15 patients (11%) and eight patients (6%), two and three infectious aetiologies were found, respectively.

Table 2. Antibiotic therapy prior to and during hospitalisation and recommendations for therapy following discharge from the hospital

	All patients (n = 133)
Prior to hospitalisation	
Treated with antibiotics (n (%))	22 (16)
Beta-lactams (n (%))	19 (14)
Macrolides/tetracyclines (n (%))	3 (2)
During hospitalisation	
Treated with antibiotics (n (%))	121 (91)
Beta-lactams (n (%))	106 (80)
Macrolides/tetracyclines (n (%))	35 (26)
Quinolones (n (%))	7 (5)
More than one antibiotic (n (%))	26 (20)
IV antibiotic therapy (n (%))	90 (68)
Days receiving IV antibiotic therapy (mean \pm SD)	2.7 \pm 1.5
Recommendations at discharge	
Antibiotic therapy prescribed (n (%))	114 (86)
Beta-lactams (n (%))	92 (69)
Macrolides/tetracyclines (n (%))	30 (23)
Quinolones (n (%))	5 (4)
More than one antibiotic (n (%))	13 (10)

Table 3. Frequency distribution of various infectious aetiologies among the 133 study patients

Pathogen	n (%)
Viral agents	
Influenza virus type A	12 (9)
Influenza virus type B	5 (4)
Parainfluenza virus type 1	7 (5)
Parainfluenza virus type 2	6 (5)
Parainfluenza virus type 3	9 (7)
Adenovirus	7 (5)
Respiratory syncytial virus	6 (5)
At least one of these viruses	52 (39)
Bacterial agents	
<i>Streptococcus pneumoniae</i>	24 (18)
<i>Hemophilus influenzae</i>	2 (2)
<i>Moraxella catarrhalis</i>	4 (3)
At least one of these bacteria	27 (20)
Atypical bacterial agents	
<i>Legionella</i> spp.	9 (7)
<i>Mycoplasma pneumoniae</i>	15 (11)
<i>Chlamydia pneumoniae</i>	3 (2)
At least one of these atypical bacteria	27 (20)
Unknown aetiology	56 (42)

The mean duration of the hospitalisations was 4.3 ± 2.6 days (range 1–38). Sixty four patients (48%) were hospitalised for up to three days, 66 patients (50%) for 4–10 days and three patients (2%) for 11–19 days. Thirteen patients (10%) were readmitted to the hospital within a month of the index hospitalisation. At the one-month follow-up appointment 19 patients (14%) said that they had not returned to their pre-morbid functional state.

Discussion

The aetiological diagnoses in our study were based almost entirely on serological 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. In order to minimise this problematic possibility we diagnosed acute infection with a specific pathogen only in the presence of a significant change in the antibody titre or level between the paired sera in one of the specific immunoglobulins. This strategy increased our confidence that the identified pathogen was indeed the aetiological cause of the RTI, but at the same time it reduced the sensitivity of the tests and is responsible, at least in part, for the unknown aetiology in 42% of the patients in this study. Diagnosis by serology was preferred over the possibility of isolating pathogens from respiratory secretions. The isolation method suffers, for some of the pathogens, from low sensitivity and even when a pathogen is isolated from the secretion, an incidental contamination cannot be ruled out. In contrast, a change in antibody titre for a specific pathogen between paired sera usually indicates a

significant association between that pathogen and the host, with a high probability that the association between the pathogen and the disease is causative.

To add strength and further validity to the study results it would have been appropriate to include a similarly-sized control group with participants who were matched by age, gender and season of the year to the study group. This was not feasible primarily because of the huge expense involved in conducting serological tests for such a control group, which was beyond the scope of the funds available for the study.

In order to determine the inclusion criteria for this study we had to define LRTI. A comprehensive survey of the definitions of LRTI (also by its other names acute bronchitis or acute tracheobronchitis) used by investigators in 22 different studies showed that the number of definitions is close to the number of studies [3]. Among all the definitions that have been proposed we chose to use Macfarlane's definition [3], which despite the problems involved in its application, seemed to be the most logical. We added to this clinical definition the requirement for absence of radiographic evidence of pneumonia in accordance with the definitions proposed by the American Thoracic Society [4].

In a comprehensive search of the literature only one study of the broad range of aetiologies of LRTI among adults in the community was found [5] with specific reference to the elderly. In that study pneumococcus was the dominant aetiology with an almost non-existent prevalence of atypical pathogens. Despite the apparent similarity between that study and the present one, it is important to note that the previous study involved non-hospitalised elderly patients in the community and included patients with CAP. The pneumococcal aetiology 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 aetiologies 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 aetiological distributions found in them.

In the present study patients with documented COPD were excluded. This decision stemmed from the consideration that elderly COPD patients comprise a unique population in terms of level of risk and frequency of respiratory tract infections. Thus, it was reasonable to assume that the frequency distribution of infectious aetiologies for acute exacerbations in this population would not necessarily be similar to LRTI in elderly patients without COPD. This assumption was confirmed in another study of ours that was published recently, which specifically evaluated the frequency distribution of infectious aetiologies in acute exacerbations of COPD [6]. A comparison of the results of these two studies

reveals a degree of similarity between the frequency distributions of infectious aetiologies in the two populations, but not an identity.

The frequency distribution for LRTI found in our study points to a clear dominance of viral aetiologies that were identified in 40% of the patients, and close to half of this rate for each of the other two groups of classic bacteria and atypical pathogens. The distribution is different from those quoted 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*' [7, 8]. We believe that the difference between those versions and the results of the present study stems from the fact that we studied elderly hospitalised patients in contrast with the broad spectrum of community patients studied in the papers referred to above. The studies also differ in the diagnostic techniques used for the identification of the various pathogens, as discussed above.

Our findings in relation to several specific aetiologies require further discussion. *C. pneumoniae* was identified in only three patients. This percentage is low in both absolute and relative terms to the rate of infections with this pathogen reported in a previous study [9]. The reason for this low rate of *C. pneumoniae* infections in the present study is that we diagnosed acute infection with this pathogen only in the presence of a significant increase in antibody titre 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* that did not change between acute and convalescence phase sera are viewed as evidence of chronic infection with this pathogen, at least in COPD patients [10]. Thus, patients with these titers were not diagnosed as acutely infected with this pathogen in the present study. If we had analysed the data using those criteria we would have identified 31 patients (23%) as serologically positive for acute *C. pneumoniae* infection.

In contrast to all other studies on the aetiologies of LRTI that identified very low and even miniscule rates of infection with *Legionella* spp., we found nine patients with this aetiology, a rate of positivity of 7%. 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 *L. pneumophila* 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 hospitalisation in intensive care units [11, 12]. In contrast, in the present study we tested 40 other serogroups of *Legionella* spp. in addition to *L. pneumophila* 1. In all nine patients there was a significant antibody response to *Legionella* spp. of serogroups other than *L. pneumophila* 1. The disease

caused by these pathogens is usually relatively mild and it is not surprising that patients with these pathogens did not have radiologic evidence of CAP and their disease course was relatively benign.

Three known respiratory tract bacteria, namely *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, were tested using an innovative serological technique that is not in routine use. Our previous experience with this technique, which was good, has been described and discussed in a previous publication [13]. The prevalence rates of LRTI with positive serology for these bacteria in the present study were relatively low. This finding contrasts strongly in particular with the results of another previous study of ours that found a positive serological rate of 46–58% for *S. pneumoniae* in elderly patients hospitalised with CAP [14]. This 3-fold difference in positive 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. This difference provides evidence for the high level of reliability of the tests and indicates that although *S. pneumoniae* is the most common aetiology among hospitalised CAP patients, its prevalence is much lower as the aetiology of non-pneumonic LRTI among elderly hospitalised patients.

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, patient composition, and geographic area. The year in which the study was conducted was not atypical in frequency of viral infections, did not have an epidemic of *M. pneumoniae* infections, the five study months did include the regular seasonal peak of influenza A and B infections in January and February and all the study patients were hospitalised from their homes in the community and not from nursing homes. Therefore, it is reasonable to assume that the distribution of aetiologies in another season of the year, in another elderly population, and even in our region, would not be identical to the results of the present study.

In 42% of the patients there was no evidence of defined infectious aetiology despite the intensive investigation of paired sera. We believe that there are two primary explanations for this finding. First, we did not include an unchanged high antibody titre between the sera as a criteria for specific aetiological diagnoses. This requirement, which is explained above, increased the diagnostic specificity but apparently reduced the sensitivity leading to the classification of unknown aetiology in some of the patients. Second, there may be other viral aetiologies, such as rhinovirus and coronavirus, which are known to cause acute bronchitis [7], but are technically difficult to diagnose serologically. It is possible that in some of the patients in our study the aetiology of LRTI was an infection with one of these viruses, although as a general rule these infections cause an afebrile illness [7] while all the patients in this study were febrile.

In one third of the patients in our study in whom an aetiology 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 [15] and has been attributed in the past to bacterial infection that is secondary to viral infection. Two studies that used advanced serological techniques to assess the aetiology of CAP in hospitalised patients reported a high rate of 38% of patients with evidence of more than one aetiology [13, 16]. Those studies, like the present one, found all possible combinations of pathogens and not only an association between bacteria and viruses. Since LRTI 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 aetiologies in CAP [13] are valid for LRTI as well.

An important, although not surprising, finding is the broad and liberal treatment of the study patients with antibiotics during the course of hospitalisation. Over 90% of the patients were treated with antibiotics in the hospital, the vast majority with beta-lactam monotherapy. In assessing this finding it should be noted that the accepted recommendation that antimicrobial treatment is ineffective for the majority of patients with acute bronchitis [17] was based on data collected in otherwise healthy adults [18], who, for the most part, were not elderly. It is also important to note that despite the proven lack of efficacy of antibiotics in the therapy of LRTI, 66–80% of patients in the primary care setting in the general population with this diagnosis are given an antibiotic prescription [19, 20]. The explanation for this paradox appears to lie in the low predictive value of the clinical manifestations of LRTI for the specific infectious aetiology of the infection. The most striking example is purulent sputum, whose presence does not allow differentiation of viral from bacterial causes [17]. The vast majority of the ambulatory population, of whom only some are elderly patients, is treated with antibiotics even though this therapy is ineffective in most of them. Thus, it is not surprising that among elderly patients who have substantial chronic co-morbidity, 91% are treated with antibiotics even though the frequency distribution of infectious aetiologies does not appear to justify this practice.

The therapeutic significance of the results of our study is not clear-cut. Although the aetiology was viral in most of the patients, they cannot be identified on clinical grounds, so it is not practical to deny antibiotic treatment to all these patients. The question of the antibiotic of choice thus arises. Classic bacterial aetiologies were found in 20% of the patients. In these patients beta-lactams are the treatment of choice. The similar percentage of atypical bacterial infections, for whom beta-lactams are not effective, supports the use of other antibiotics, including macrolides, tetracyclines and quinolones, even though the disease is self-limited in at least some of these patients and antibiotic therapy does not affect its course. The possibility of combining two types of antibiotics as recommended for CAP might seem

logical, but requires convincing proof from clinical trials that specifically address this issue.

Conclusion

In hospitalised elderly patients LRTI is caused by a broad spectrum of aetiological agents, of which respiratory viruses are dominant, with a lower but important prevalence rate for both classical and atypical bacteria. A substantial proportion of patients have serological evidence of infection with more than one pathogen. Despite this frequency distribution the vast majority of these patients are treated with beta-lactams. The issue of antibiotic therapy for these patients and the antibiotics of choice should be addressed in additional studies designed to specifically evaluate these questions.

Key points

- Non-pneumonic LRTI is caused in hospitalised elderly patients by a broad spectrum of aetiological agents, primarily respiratory viruses with a significant, though lesser, prevalence of classical and atypical bacteria.
 - Despite this distribution of aetiologies, most patients are treated with beta-lactam antibiotics.
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