Etiology and Clinical Characteristics of Patients with Acute Respiratory Infections treated in the Department of Infectious Diseases in 2015-2016

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Abstract

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Title
Etiology and Clinical Characteristics of Patients with Acute Respiratory Infections treated in the Department of Infectious Diseases in 2015-2016

Aim
To characterise influenza virus negative patients with severe acute respiratory infections (SARIs) treated in the Infectious Diseases (ID) and Geriatrics department (GD) within the Lithuanian University of Health Sciences (LSMU) during the 2015-2016 influenza season.

Objectives
1. To verify the etiology of non-influenza patients with SARIs.
2. To describe the demographic and clinical characteristics of non-influenza patients with SARIs.
3. To analyze the treatment and outcome of non-influenza patients with SARIs.

Methods
The study population was taken from the test-negative case-control study, conducted between 1 December 2015 and 1 May 2016, which measured seasonal influenza vaccine effectiveness against laboratory confirmed influenza. Data on demographic and clinical characteristics was gathered by medical records. All previous conducted tests such as; hematological tests, blood cultures, sputum cultures, serology, and chest radiographs were done in discretion of the treating physician at the time of patient’s hospitalization. Influenza along with other respiratory viruses were confirmed by multiplex reverse transcription polymerase chain reaction (RT-PCR), bacterial etiology of SARI was established by blood and/or sputum culture and/or Mycoplasma and Chlamydia serology.

Results
Eighty-three out of 125 (66.4%) patients were negative for any influenza virus infection and were included into the study. The case records of 74 patients (89.1%) were available for the retrospective analysis. These patients were diagnosed with either acute bronchitis (11/74, 14.8%), pneumonia (58/74, 78.3%), or chronic obstructive pulmonary disease (COPD) /asthma exacerbation (5/74,
6.7%). A viral respiratory pathogen was found by RT-PCR in 18 subjects (18/74, 24.3%). A sputum culture confirmed a bacterial pathogen in 5 SARI patients with no co-infections with other respiratory viruses (5/74, 6.7%). In 51 patients (68.9%), the specific etiology was not established. According to our definition, a presence of lung infiltration found on chest radiograph was diagnosed as pneumonia (100%). In acute bronchitis, eight subjects (72.7%) complained of sore throat, which was significantly more often compared to patients with pneumonia or COPD/asthma exacerbation. For COPD/asthma exacerbation, functional deterioration was uppermost at 80.0% unlike pneumonia and acute bronchitis, however, it was not considered severely significant as an index for COPD/asthma exacerbation. Over half of patients with acute bronchitis were prescribed oseltamivir as treatment (54.5%). A significant number of patients with acute bronchitis (72.7%), pneumonia (100%), and COPD/asthma exacerbation (100%) were given antibiotics.

**Conclusion**

Due to the majority of the study subjects with no established specific etiology, better diagnostic methods for SARI etiology are suggested. Furthermore, there were no significant differences of demographic and clinical characteristics detected among acute bronchitis, pneumonia and COPD exacerbation groups, except that more cases of acute bronchitis were seen to be more obese. Lastly, oseltamivir treatment may be prescribed in severe cases of SARI without the necessity of routine RT-PCR testing due to its high-cost in Lithuania and low evidence of influenza resistance to oseltamivir. Antibiotic therapy should be managed and accurately prescribed in order to avoid resistance in the future.

**Keywords**

acute respiratory infection, acute bronchitis, pneumonia, chronic obstructive pulmonary disease, asthma, antibiotics, infiltrate

**Conflict of Interest**

There were no reports of conflicts of interest such as sponsors, suppliers of materials, or funding during this study.
Abbreviations

ARI- Acute respiratory infection
SARI- Severe acute respiratory infection
RT-PCR- Reverse transcription polymerase chain reaction
WHO- World Health Organization
IgM- Immunoglobulin M
RSV- Respiratory syncytial virus
COPD- Chronic obstructive pulmonary disease
CAP- Community-acquired pneumonia
CDC- Centre for Disease Control and Prevention
CRP- C-reactive protein
CXR- Chest x-ray/radiograph
CT- Computerized tomography
IC- Informed consent
BMI- Body mass index
LSMU- Lithuanian University of Health Sciences
Introduction

Acute respiratory infections (ARIs) are a major cause of morbidity, hospitalization, and mortality throughout the world affecting young infants, small children under five years of age, the elderly and persons with impaired respiratory tract reserves or co-morbidities. Firstly, they are divided by upper and lower respiratory system infections. Examples of upper respiratory infections include acute pharyngitis, acute otitis media, sinusitis and the common cold. Lower respiratory infections consist of bronchitis, bronchiolitis, and pneumonia to name a few. According to data from the World Health Organization (WHO), lower respiratory infections remain the deadliest communicable disease causing 3.2 million deaths worldwide in 2015. While it is apparent that respiratory infections can lead to serious illness and even fatality, they are unfortunately often difficult to diagnose and differentiate due to their nonspecific and overlapping symptoms. Advanced diagnostic testing can also be costly and not widely available, especially in resource-poor settings. Therefore, several investigators have attempted to design criteria by means of clinical characteristics to improve the detection of severe acute respiratory infections (SARIs), such as pneumonia, from other self-limiting respiratory diseases. Corresponding to clinical guidelines, the gold standard for diagnosing pneumonia is the presence of lung infiltrates indicated by chest radiography. A diagnostic study of pneumonia in adults in general practice found inconsistency in the radiologists’ interpretation of the same chest radiograph, yet chest radiography is considered the best way to distinguish pneumonia from other respiratory tract infections. However, as a result, patients with unresolved chest infections may be labeled as having pneumonia in order to justify antibiotic prescriptions, despite guidance which advises against routine antibiotic use in patients with ARIs such as acute bronchitis or exacerbation of chronic obstructive pulmonary disease (COPD). According to guidelines, chest infection is divided into acute bronchitis (for which antibiotics are not recommended) and pneumonia (for which antibiotics are recommended). The effectiveness of antibiotic treatment in reducing the risk of complications of pneumonia has already been validated in several studies, however, the use of antibiotics to reduce the risk of serious complications for acute bronchitis or COPD/asthma exacerbation is generally not justified. Given the emergency of antibiotic-resistant strains of bacteria such as Streptococcus pneumoniae and Haemophilus influenza, it is extremely important to diagnose and
treat pneumonia accurately. Recommendations not to prescribe antibiotics are based on concerns about the development of antimicrobial resistance.

Influenza and other respiratory viruses such as respiratory syncytial virus (RSV), rhinovirus, parainfluenza virus, adenovirus, and human metapneumovirus are common causes of respiratory infections. While often manifesting as a mild illness, these viruses can result in serious complications, hospitalizations, and deaths. Identifying the viral etiology of respiratory infections has applications in both clinical management and surveillance. Early diagnosis may allow timely initiation of appropriate treatment, such as with oseltamivir management for influenza A or B, and rapid confirmation of an outbreak can lend itself to control and mitigation efforts for influenza.

While specific therapeutic or preventative measures for most viral respiratory agents (other than influenza) are lacking, diagnosis can still help in ruling out other causes of respiratory illness and facilitate implementation of appropriate infection control measures in healthcare settings.

Reverse transcriptase-polymerase chain reaction (RT-PCR), which detects viral nucleic acid by use of amplification techniques, is now considered as the gold standard assay for detection of respiratory viruses, and also has the advantage of short turn-around times as compared to methods based on virus culture and isolation. Moreover, multiplex RT-PCR assays, which allow for rapid detection of multiple types of known viral agents, are now more often used throughout the world.

The aim of this study was to characterise influenza virus negative patients with severe acute respiratory infections (SARIs) treated in the Infectious Diseases (ID) and Geriatrics department (GD) within the Lithuanian University of Health Sciences (LSMU) during the 2015-2016 influenza season. The results of this study may help to improve timely and more accurate diagnosis, inform treatment plans, establish baselines of infection, identify outbreaks, and help prioritize future treatments.

Aims and Objectives

Aim
To analyze clinical characteristics of influenza virus negative patients with severe acute respiratory infections (SARIs) treated in the Infectious Diseases (ID) and Geriatrics department (GD) within the Lithuanian University of Health Sciences (LSMU) during the 2015-2016 influenza season.

Objectives

1. To verify the etiology of non-influenza patients with SARIs.
2. To describe the demographic and clinical characteristics of non-influenza patients with SARIs.

3. To analyze the treatment and outcome of non-influenza patients with SARIs.

**Materials and Methods**

**Ethics Statement**

This research study did not involve any health-related patient interventions. It was conducted in accordance with Lithuanian legislation. Lithuanian University of Health Sciences Biomedical Research Ethics Committee (Kaunas, Lithuania) approval Nr. BEC-MF-136, dated 15 December 2017, was received respectively. Written consent forms were not required in part of this study as clinical information was anonymously analyzed from past medical files of participated patients.

**Study population and Recruitment**

The study population was taken from the test-negative case-control study, conducted between 1 December 2015 and 1 May 2016 \(^5\), which measured seasonal influenza vaccine effectiveness against laboratory confirmed influenza. The subjects were recruited from two participating sites: 1) the Department of Infectious Diseases and 2) the Department of Geriatrics of the Lithuanian University of Health Sciences, Kaunas. The population of the previous study \(^5\) consisted of individuals ≥65 years of age and patients with co-morbidities who were admitted to the participating sites due to Severe Acute Respiratory Infection (SARI) during the 2015-2016 influenza season. Patients were eligible to be included in the study when they were hospitalized for at least 24 hours, but no longer than 48 hours, had a swab taken ≤7 days after self-reported disease onset, and were not hospitalized for any influenza virus in the current season before the inclusion \(^5\). Enrolled study patients were suffering from SARI with at least one of the systemic symptoms (fever, malaise, myalgia, headache), deterioration of functional or general status, and at least one of the respiratory symptoms (cough, sore throat and shortness of breath) \(^5\). Patients not eligible to be included in this study were those previously institutionalized, unwilling to participate, and uncommunicable.
Eligible patients were asked to provide one throat and one nose swab specimen for influenza and other respiratory viruses for testing by multiplex reverse transcription polymerase chain reaction (RT-PCR). Swabbing was done after the information on demographic and clinical characteristics was collected from the medical history and patient self-report. The nasal and throat swabs were tested for influenza RNA from the isolated samples using an automatic magnetic particle method based on the standard protocol from the Centre for Disease Control and Prevention (CDC) recommendations. A total of 142 patients were included into the seasonal influenza vaccine effectiveness study. Of those, 125 patients gave informed consent (IC). Through RT-PCR, 83 patients tested negative for influenza virus and were taken as the population for this particular study. The case records of 74 patients (89.1%) were available for the retrospective analysis.

Methods
For the verification of the etiology of non-influenza SARI patients, the following microbiological methods were used:
1. Multiplex RT-PCR for the detection of 6 respiratory viruses (coronavirus, respiratory syncytial virus (RSV), adenovirus, metapneumovirus, parainfluenza virus and rhinovirus) from throat and nasal swabs (n=74).

2. Sputum cultures under suspicion of bacterial cause of SARI (n=19). Sputum specimens were cultured only if more than 25 polymorphonuclear leukocytes and fewer than 10 squamous epithelial cells were present per low-power field on results of Gram stain.

3. Blood cultures under suspicion of bacterial cause of SARI (n=16). Blood cultures were performed using automated blood culture systems.

4. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* immunoglobulin M (IgM) detection in serum by ELISA method in case of suspected atypical etiology of SARI (n=5).

**Definitions of acute respiratory tract infection**

Standardized definitions of three influenza-negative SARI infections were used in this study.

1. **Acute bronchitis** was defined as a self-limited inflammation of the large airways of the lung, that was characterized by cough after pneumonia was ruled out by chest x-ray ⁶.

2. **Pneumonia**, an inflammatory condition of the lung primarily affecting the alveoli, was defined by the presence of compatible radiological findings (specifically infiltration), and two of the following symptoms or signs: new or increased cough, new or increased sputum production, pleuritic chest pain, fever (>38°C), new or increased chest examination findings, new or increased shortness of breath or respiratory rate of greater than 25 breaths per minute or worsening functional status ⁷.

3. **Acute exacerbation of chronic obstructive pulmonary disease (COPD)**, also known as acute exacerbations of chronic bronchitis (AECB), was defined as a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) that typically lasts for several days ⁸.

**Clinical specimens and data collection**

Clinical information including age, sex, body mass index (BMI), presenting signs and symptoms, history of illness, concomitant diseases (cardiovascular, respiratory, renal, rheumatological, endocrine diseases and diabetes, haematological and non-haematological cancer, immunodeficiency and transplantation, dementia, stroke, anaemia), obesity (BMI≥30), Barthel index score, vital signs, haematological test results including C-reactive protein (CRP), clinical course, and treatment were gathered through medical record abstraction.
Standardized interpretation of radiographs
Chest radiographs (CXRs) were performed when indicated as part of routine clinical care (n=74). The images were reviewed and interpreted independently by radiologists working in Kaunas Clinical Hospital. Signs included end-point consolidation, other consolidation/infiltrate, no consolidation/infiltrate/effusion or uninterpretable. Infiltrate is defined as any pathologic density in the lung. Consolidation is especially dense, often homogeneous, confluent alveolar infiltrate that sometimes may encompass an entire lobe or large segment, fluffy, mass-like, cloud-like density, erases heart and diaphragm borders (silhouette sign); often contains air bronchograms. End-point consolidation is a dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air bronchograms and sometimes associated with pleural effusion. No consolidation/infiltrate/effusion is the absence of end point consolidation, other infiltrate or pleural effusion. Lastly, uninterpretable is classified if the features of the image are not interpretable in terms of presence or absence of “primary end-point” without additional images. No further reading should be made for such images.

Statistical analysis
The data was analyzed with SPSS statistics software for Windows version 12.0 (SPSS Inc., Chicago, IL). Comparisons and analysis of differences of demographic and clinical variables across the study groups were made using chi-square homogeneity tests and analysis of variance (ANOVA). Within each cohort, comparisons of clinical variables among patients with either acute bronchitis, pneumonia, or COPD/asthma exacerbation were made. For all of the statistical tests, p<0.05 was considered statistically significant.

Results
Overall, 125 patients with IC were included from the previous seasonal influenza vaccine effectiveness study. A total of 83 (66.4%) patients were negative for any influenza virus infection. Amongst those tested as negative with influenza, twelve patients were subsequently excluded due to non-respiratory or unknown final diagnoses. The 74 subjects were available for analysis in this study and, according to our definitions, were divided into 3 groups by acute bronchitis (n=11, 14.8%), pneumonia (n=58, 78.3%), or COPD exacerbation/asthma (n=5, 6.7%).

Etiology of non-influenza SARI patients
A viral respiratory pathogen was found by RT-PCR in 18 non-influenza SARI subjects (18/74, 24.3%). From these viruses, six were RSV (33.3%), five were rhinovirus (27.7%), four were
human metapneumovirus (22.2%), two were adenovirus (11.1%), and one was parainfluenza virus (5.5%). A sputum culture confirmed a bacterial pathogen in 5 SARI patients with no co-infections with other respiratory viruses (6.7%). Blood cultures were performed for 16 SARI cases but returned as negative in all cases. Serology for IgM antibodies of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in suspected atypical cases were tested in 5 patients (n=5) with pneumonia, however, returned with no detection. In 51 subjects of this study (68.9%), the specific etiology was not established.

**Figure 2.** Etiology according to pathogen of non-influenza SARI patients (n=74)

![Etiology Chart]

Forty-three (74.1%) patients with diagnosed pneumonia did not have a confirmed viral or bacterial cause detected by RT-PCR or bacterial sputum culture, respectively. Among the viruses, metapneumovirus (4/11, n=4), RSV (2/11, n=2), rhinovirus (2/11, n=2), and adenovirus (3/11, n=3) were found in patients with diagnosed pneumonia. Sputum cultures grew *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Acinetobacter* with *Staphylococcus aureus*, *Escherichia coli* and *Haemophilus influenzae* bacteria with no co-infection with viruses. Etiology of patients with acute bronchitis consisted of either a virus (n=5) or unknown (n=6). The viruses detected in those with acute bronchitis were parainfluenza (1/5, n=1), adenovirus (1/5, n=1), RSV (1/5, n=1), and rhinovirus (2/5, n=2).
One case in a patient diagnosed with COPD/asthma exacerbation had a positive sputum culture for *H. influenzae*. Viral etiology in COPD/asthma exacerbation included rhinovirus (1/2, n=1) and RSV (1/2, n=1).

**Demographic and clinical characteristics of non-influenza SARI patients**

Table 1 displays demographic and inflammatory marker variables; C-reactive protein (CRP) levels, age, body mass index (BMI) and Barthel index in each group of acute bronchitis, pneumonia, and COPD/asthma exacerbation.
Table 1. Comparison of demographic and clinical variables across three groups of non-influenza SARI

<table>
<thead>
<tr>
<th></th>
<th>Acute bronchitis (n=11)</th>
<th>Pneumonia (n=58)</th>
<th>COPD/Asthma exacerbation (n=5)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. dev.</td>
<td>Mean</td>
<td>Std. dev.</td>
</tr>
<tr>
<td>BMI</td>
<td>32.400&lt;sub&gt;a&lt;/sub&gt;</td>
<td>5.50</td>
<td>27.498&lt;sub&gt;b&lt;/sub&gt;</td>
<td>5.82</td>
</tr>
<tr>
<td>Age</td>
<td>64.27&lt;sub&gt;a&lt;/sub&gt;</td>
<td>15.82</td>
<td>69.02&lt;sub&gt;a,b&lt;/sub&gt;</td>
<td>16.03</td>
</tr>
<tr>
<td>CRP</td>
<td>104.43</td>
<td>114.23</td>
<td>126.80</td>
<td>91.94</td>
</tr>
<tr>
<td>Barthel</td>
<td>100.00</td>
<td>0.00</td>
<td>95.00</td>
<td>11.20</td>
</tr>
</tbody>
</table>

Each subscript letter denotes a subset of Diagnosis categories whose columns proportions do not differ significantly from each other at the .05 level.

*<sup>a</sup> vs. <sup>b</sup> shows statistical difference between groups
*<sup>a</sup> vs. <sup>a,b</sup> or <sup>b</sup> vs. <sup>a,b</sup> does not show statistical difference between groups

Patients with acute bronchitis had a slightly higher BMI than those diagnosed with pneumonia or COPD/asthma exacerbation (P=0.020). Furthermore, age was significant in those with COPD/asthma exacerbation compared to diagnoses with pneumonia and acute bronchitis, reaching an over 10-year age gap. CRP levels and Barthel index did not show a statistical difference among these groups, although patients with COPD/asthma exacerbation had the lowest CRP-level compared to pneumonia and acute bronchitis.

Table 2 exhibits systemic (fever, malaise, headache, myalgia) and respiratory (sore throat, cough, shortness of breath) symptoms along with the sudden onset of disease, general or functional status deterioration, lung infiltration found on chest x-ray, Barthel index score of <100 points, and concomitant diseases known and recorded according to subject.

Table 2. Clinical characteristics and comorbidities among cases in the total sample during the 2015-2016 influenza season
Of systemic and respiratory symptoms, sore throat and functional deterioration of status were among the only significant differences between the three groups. Sore throat was presented in more patients with acute bronchitis than those with pneumonia. However, this was not the case with patients diagnosed with COPD/asthma exacerbation, which showed no clinical significance.
between the two. Those with COPD/asthma exacerbation portrayed the most with functional deterioration ($P=0.106$). Lung infiltrates on chest x-ray were only seen in patients with diagnosed pneumonia (100% ; this was the main criteria for pneumonia diagnosis). As for comorbidities, patients diagnosed with COPD/asthma exacerbation had a significant underlying history of cardiovascular disease (100%), dementia or strokes (80.0%) than those hospitalized with pneumonia or acute bronchitis. Obesity was detected (63.6%) in more patients with acute bronchitis.

Table 3 shows antibiotic therapy and CRP levels among the three groups; acute bronchitis, pneumonia, and COPD/asthma exacerbation based on their etiology.

**Table 3.** Comparison of C-reactive protein values and antibiotic therapy among different etiologies found in the three groups of non-influenza SARI

<table>
<thead>
<tr>
<th></th>
<th>Acute Bronchitis (n=11)</th>
<th>Pneumonia (n=58)</th>
<th>COPD/Asthma exacerbation (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotic Therapy</strong></td>
<td>n</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Viral (n=5)</td>
<td>4</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Bacterial (n=0)</td>
<td>-</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>Unknown (n=6)</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.621</td>
<td>0.254</td>
<td>0.254</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>81.72</td>
<td>95.15</td>
<td>36.15</td>
</tr>
<tr>
<td>St. Dev</td>
<td>57.89</td>
<td>74.73</td>
<td>19.25</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>118.87</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92.60</td>
<td>99.84</td>
</tr>
</tbody>
</table>

All patients hospitalized with pneumonia or COPD/asthma exacerbation were given antibiotic treatment, including those with viral and unknown origin. The CRP levels were consistently more elevated in terms of bacteriological etiology than of viral etiology in patients with pneumonia and COPD/asthma exacerbation.

**Treatment and outcome of non-influenza SARI patients**

Table 4 portrays treatment of either antibiotic or antiviral therapy among groups of acute bronchitis, pneumonia, and COPD/asthma exacerbation.
Table 4. Treatment among the three group samples of SARI

<table>
<thead>
<tr>
<th></th>
<th>Acute Bronchitis (n=11)</th>
<th>Pneumonia (n=58)</th>
<th>COPD/Asthma exacerbation (n=5)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Therapy</td>
<td>N: 8a; %: 72.7%</td>
<td>N: 58b; %: 100.0%</td>
<td>N: 5ab; %: 100.0%</td>
<td>0.000</td>
</tr>
<tr>
<td>Oseltamivir Therapy</td>
<td>6; 54.5%</td>
<td>16; 27.6%</td>
<td>1; 20.0%</td>
<td>0.179</td>
</tr>
</tbody>
</table>

*a vs. b shows statistical difference between groups
*a vs. a,b or b vs. a,b does not show statistical difference between groups

All patients with diagnosed pneumonia or COPD/asthma exacerbation received antibiotic therapy as treatment during the time of their hospitalization, which showed exceeding significance (P=0.000). Over half of patients with acute bronchitis were prone to receiving oseltamivir as therapy (54.5%) than those with diagnosed pneumonia or particularly COPD/asthma exacerbation. In the total sample, one out of 74 patients died during the hospitalization (1.3%), of which diagnosis was pneumonia. No patients were transferred to the Intensive Care Unit (ICU) or ventilated.

**Discussion**

This study aimed to analyze clinical characteristics of influenza virus negative patients with SARI during the 2015-2016 influenza season. The SARI included acute bronchitis, pneumonia, and COPD/asthma exacerbation. Based on etiology, a viral respiratory pathogen was discovered in 18 non-influenza SARI subjects (18/74, 24.3%). From these viruses, six were RSV (33.3%), five were rhinovirus (27.7%), four were metapneumovirus (22.2%), two were adenovirus (11.1%), and one was parainfluenza virus (5.5%). A bacterial pathogen, confirmed by sputum culture, was found in 5 SARI patients (6.7%). All blood cultures performed for 16 SARI cases returned as negative. Serology for IgM antibodies of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in suspected atypical cases were tested in 5 patients (n=5) with pneumonia, however, returned with no detection. Lastly, the majority of the study subjects (n=51, 68.9%) did not have an established specific etiology. While multiplex RT-PCR testing is a well-known high-quality method of diagnosis, many of our cases resulted in no specific etiology. Therefore, further improvement of microbiological diagnosis is needed.
Diagnosing community-acquired pneumonia (CAP) from acute bronchitis or COPD/asthma exacerbation solely from presenting symptoms is a proven challenge. For example, many patients with an ARI present with cough as a primary symptom. According to our current study, 55 patients (94.8%) presented with cough of those diagnosed with pneumonia, 10 patients (90.9%) of acute bronchitis and 5 (100.0%) patients of COPD/asthma exacerbation. Furthermore, patients in all three groups experienced general deterioration in their health status. Sore throat was also found in more patients with acute bronchitis (72.7%) than those with pneumonia and COPD/asthma exacerbation. Other systemic or respiratory symptoms were considered not significant in comparison. Normally, clinical findings are not definitive, however, some may increase the likelihood of pneumonia. A 1997 JAMA study by Metlay et al. showed that historical features of fever, chills, and myalgias all made the diagnosis of pneumonia somewhat more likely while presence of runny nose and sore throat made the diagnosis of pneumonia less likely.

In our definition, CAP was diagnosed in patients with specifically a presence of infiltrate on chest x-ray (CXR) and two of the following symptoms or signs: fever (>38°C), new or increased cough, sputum production, dyspnea, pleuritic chest pain, crackles or signs of consolidation on chest auscultation, new or increased shortness of breath or respiratory rate of greater than 25 breaths per minute and worsening of functional status. Many clinicians and radiologists state that a chest radiograph with infiltrate compatible with acute pulmonary infection usually “clinches” the diagnosis of CAP. In four prospective cohort trials to evaluate the sensitivity and specificity of clinical history and physical examination in pneumonia, found by Metlay and colleagues, the reference standard for the diagnosis of pneumonia was new infiltrate on chest radiograph. While positive chest x-rays may be considered the “standard” for diagnosing pneumonia, they are not as sensitive for diagnosing pneumonia as some would believe. In one 2008 Journal of Emergency Medicine study, plain chest radiographs, which were shown as normal, missed 27% of pneumonia cases that were later diagnosed on chest computerized tomography (CT). Another 2006 American Journal of Emergency Medicine study, presented at the 2005 American College of Emergency Physicians (ACEP) Research Forum, stated that 17.7% of normal chest x-rays later showed pneumonia on CT scans. An additional study expressed that overall reliability for the presence of any infiltrate is considered moderate. This is driven by the low reliability and variability around the radiographic diagnosis of interstitial infiltrates. Possible differential diagnoses upon findings of infiltrate on CXRs are pulmonary empyema, tuberculosis, and non-cardiosis.
Radiological changes that may indicate a more accurate diagnosis of pneumonia are lobar consolidation and consolidation with infiltration, instead of a sole finding of inflammatory infiltrates. Furthermore, laterolateral chest radiographs may increase the diagnostic accuracy of lung consolidation and, therefore, of pneumonia. A CT scan can also give additional information in indeterminate cases, however, it is more expensive, has a higher dose of radiation, and cannot be done at bedside. In our current study, lung infiltration found on CXR was used as the main criteria for diagnosis of pneumonia since analysis and comparison of other clinical characteristics would have been prone to be difficult. In addition, the etiology usually cannot be determined based on CXR, however, some studies suggest that lobar consolidation, cavitation, and pleural effusions are commonly found when caused by a bacterial pathogen. Radiographs of viral pneumonia may appear normal, appear hyper-inflated, have bilateral patchy areas, or present similar to bacterial pneumonia with lobar consolidation.

Raised infectious biomarkers such as C-reactive protein (CRP) are suggestive of an infectious etiology. In our laboratory testing, the mean CRP for pneumonia was 126.80 mg/L, however, it was not statistically significant compared to the CRP levels of acute bronchitis or COPD/asthma exacerbation. CRP as a single predictor of CAP in patients with respiratory symptoms has been debated and evaluated in several studies. According to one study, a CRP level of 50.0 mg/L or greater is modestly helpful when positive for diagnosis of pneumonia, but it is important to note that normal values do not rule it out. Additionally, another study found that CRP was significantly elevated in bacterial infection and was both sensitive and specific for bacterial infection. The data demonstrated that with a CRP level of less than 20 mg/L, this makes the diagnosis of bacterial infection extremely unlikely, whereas a CRP level greater than 80 mg/L, should signal an active bacterial process. This is important since differentiating bacterial from viral infections can be challenging, especially during the influenza season. In our study, the lowest mean CRP value was 36.15 mg/L in those diagnosed with viral-caused COPD/asthma exacerbation. In addition, the mean CRP level found in COPD/asthma exacerbation caused by bacteria was 71.70 mg/L. Patients with pneumonia or acute bronchitis, caused by either a virus, bacteria or unknown etiology, all had CRP levels higher than 80 mg/L. Overall, a CRP level is a useful clinical tool for pneumonia and other infectious diseases, however, it should not be solely relied upon. Nevertheless, a highly elevated CRP usually does suggest bacterial etiology which may help in more accurate prescription of antibiotic medication. More recently, pro-
adrenomedullin (ADM), presepsin (soluble CD14-subtype; sCD14-ST), pro-atrial natriuretic peptide (ANP), and copeptin have been reported as new biomarkers that reflect the severity and extensiveness of pneumonia than nonspecific CRP \(^{18}\).

Many studies argue that blood cultures are typically not recommended for most hospitalized patients with CAP and should only be performed when there is severe illness or when an atypical cause is suspected. According to literature, the most common blood isolate in patients with CAP is *S. pneumoniae*, which is positive in about 20 to 25 percent of inpatients. Although a blood culture can enable a specific microbiological diagnosis with a lower probability of false-positive cultures than with bronchial samples, there is extremely low cost-benefit of blood cultures in patients hospitalized for moderate CAP and treated with antibiotics before admission. A study comparing 125 patients with CAP caused by pneumococcal bacteremia and 1,847 patients with nonbacteremic CAP found no increase in poor outcomes among those with bacteremia \(^{19}\). There has also been a link to a prolonged duration of hospitalization in those with an obtained blood culture, which may lead to secondary nosocomial infection. According to our results, all blood cultures drawn (n=16) were negative for bacteremia or septicemia. Therefore, as other studies state, drawing of blood cultures may not be necessary in majority of patients as blood culture positivity rate is relatively low, regardless of bronchial sputum cultures, there is still a high rate of false-positive blood cultures, and positive cultures rarely lead to modification or narrowing of antibiotic therapy. Some studies have suggested that sicker patients (as judged by the pneumonia severity index [PSI]) should be tested by blood culture \(^{20}\), as they are more likely to be positive, along with those who require admission to the ICU for CAP. Nevertheless, in other patients, blood cultures should typically be considered optional.

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend that sputum specimens be obtained before the initiation of antibiotic therapy in inpatients \(^{21}\). A negative sputum culture result from a good-quality sample (positive for neutrophils, but <25 epithelial cells per low-power field) is strong evidence that gram-negative bacilli and *Staphylococcus aureus* are absent and can prompt safe de-escalation of antibiotic therapy. Furthermore, purulent sputum is not predictive of pneumonia.

Acute and convalescent-phase serologic testing is the standard for other atypical causes of pneumonia \(^{21}\). Two atypical causes of pneumonia that were tested in this study were *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Only 3 to 10 percent of persons infected with *M.*
Some patients develop pneumonia. Since *M. pneumoniae* infections become more common with increasing age, it is particularly important to consider this agent in elderly patients. As for *C. pneumoniae*, the antibody is present in 75 percent of elderly persons. It is more likely to occur in older patients with comorbid diseases than in those who are otherwise healthy. However, treating patients based on a positive acute-phase titer result has been shown to be unreliable. Many atypical etiologies of pneumonia can be treated with empirical antibiotic management, also given for typical causes such as *S. pneumoniae*. Therefore, serology for other atypical pathogens should not be routinely ordered unless highly suspected.

Oseltamivir (Tamiflu), an antiviral medication, is indicated for treatment and prevention in patients with influenza A and influenza B (flu) virus. It works as a neuraminidase inhibitor, a competitive inhibitor of influenza’s neuraminidase enzyme. Recommendations regarding oseltamivir treatment are becoming controversial as are criticisms of the recommendations. In our study, 54.5% of patients with acute bronchitis, not caused by influenza according to RT-PCR, were prescribed oseltamivir as treatment. For patients with diagnosis of pneumonia, 27.6% were prescribed oseltamivir and 20.0% of those with COPD/asthma exacerbation.

Generally, according to the CDC, oseltamivir should be recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized, has severe, complicated or progressive illness, or is at higher risk for influenza complications. According to one data of a study, oseltamivir had a more satisfactory effect towards patients who had tested positive for influenza on a laboratory test, unlike patients with flu-like symptoms who subsequently were found to not have the flu. Therefore, a rapid response and confirmation by RT-PCR testing for influenza is important for clinicians to precisely prescribe oseltamivir as clinical benefit is greatest on early administration, within 48 hours of the influenza illness onset.

On the other hand, current CDC data, as of February 2018, only shows a 1% resistance rate with oseltamivir and peramivir for influenza A strain H1N1 pdm09 and zero percent resistance rate for these drugs with another strand of influenza A. As RT-PCR testing is more exorbitant, according to the Minister of Health of the Republic of Lithuania, and given the fact that there has been low evidence of antiviral resistance currently to oseltamivir among circulating influenza viruses, antiviral medications can be distributed to patients with severe cases of SARI without the necessity of routine RT-PCR.
Antibiotics are prescribed at more than 100 million adult ambulatory care visits annually, and 41% of these prescriptions are for respiratory conditions. Inappropriate antibiotic use for ARI is an important contributor to antibiotic resistance, which is an urgent public health threat. For example, acute bronchitis leads to more inappropriate antibiotics prescribing than any other ARI syndrome in adults. A systemic review of 15 randomized, controlled trials found limited evidence to support the use of antibiotics for acute bronchitis and a trend toward increased adverse events in patients treated with antibiotics. A randomized, placebo-controlled trial comparing ibuprofen, amoxicillin-clavulanic acid, and placebo showed no significant differences in the number of days to cough resolution. Although macrolides (azithromycin) are frequently prescribed for patients with a cough, one study showed that patients with acute bronchitis treated with a macrolide had significantly more adverse events than those receiving placebo.

In our current study, 8 patients (72.7%) of those with acute bronchitis were prescribed with antibiotics. However, since there is no shown benefit of antibiotics, patients may benefit more strongly from symptomatic relief instead, such as with cough suppressants (dextromethorphan or codeine), expectorants (guaifenesin), first-generation anti-histamines (diphenhydramine), decongestants (phenylephrine), and β-agonists (albuterol), although data to support specific therapies are limited. Furthermore, over-the-counter symptomatic relief has a low incidence of minor adverse effects, including nausea, vomiting, headache, and drowsiness.

Due to the fact that the exact causative organism is not identified in many patients with CAP, as our results showed, treatment is usually empiric. One of the major differences between U.S. and European guidelines for treatment of CAP is that all patients in the United States receive treatment for S. pneumoniae and atypical organisms because CAP is more often caused by these pathogens in North America. Furthermore, it is important to educate all patients about smoking cessation and moderation of alcohol use, and provide information about rest, nutrition, hydration, follow-up, and the importance of pneumococcal and influenza vaccination.

To increase patient satisfaction and decrease antibiotic prescriptions for ARI, an evidence-based strategy is offered. Clinicians can promote appropriate antibiotic use by labeling acute bronchitis as a “chest cold” or “viral upper respiratory infection” and providing patient information sheets about appropriate antibiotic use and alternatives to antibiotics for managing symptoms. A recent study showed an 85% decrease in antibiotic prescribing for ARI and increased satisfaction ratings when providers gave advice on symptomatic therapy and explained why antibiotics were
not needed for ARI 30. A symptomatic prescription pad can be used to provide recommendations for management of symptoms, allowing patients to walk away with a plan of action. When it is unclear whether an antibiotic is needed, delayed or postdated antibiotic prescriptions (also known as the wait-and-see approach) offer the possibility of future antibiotic treatment if the condition does not improve. This approach has also been shown to increase patient satisfaction and decrease antibiotic use 31.

Reducing antibiotic prescriptions on a large scale will require a multidimensional approach. A community-level, randomized trial in Massachusetts showed that implementing a multichannel intervention that includes targeting physician behavior, small-group education, disseminating educational materials to the community, and providing provider prescribing feedback in various settings further decreases antibiotic prescription rates 32. In addition to education, examples of provider-level interventions that have been shown to be effective include audit and feedback and clinical decision support 33. Reducing inappropriate antibiotic prescribing will improve quality of care, decrease health care costs, and preserve the effectiveness of antibiotics in the future.

This study is subject to several limitations. The main limitation is the sample size of non-influenza SARIs treated in the Infectious Diseases and Geriatrics Department of LSMU during one influenza season. Our data represents only one city and therefore, this may not provide an accurate representation of those affected by non-influenza SARIs and their clinical characteristics in the country. Large-scale prospective surveillance studies are required to provide more accurate information about respiratory infection etiology as well as help develop prediction rules, which could favorably influence clinical outcomes as well as antibiotic management.

**Conclusion**

1. In this study, a viral respiratory pathogen was discovered in a quarter of SARI subjects, a bacterial pathogen was found in less than a tenth, and the majority of the study subjects did not have an established specific etiology. These results could suggest that better diagnostic methods for SARI etiology are needed.

2. No significant differences of demographic and clinical characteristics were detected among acute bronchitis, pneumonia and COPD exacerbation groups, except that the cases of acute bronchitis were more obese and were detected with cardiovascular comorbidities less often.
3. Pneumonia and COPD/asthma exacerbation patients were treated with antibiotics significantly more often than acute bronchitis patients, while over half of patients with acute bronchitis received Oseltamivir. Mortality of non-influenza SARI patients was fortunately low (1.3%).
References


