Bacterial Complications of Respiratory Tract Viral Illness: A Comprehensive Evaluation

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Background. Respiratory tract infection is one of the most common reasons for hospitalization among adults, and recent evidence suggests that many of these illnesses are associated with viruses. Although bacterial infection is known to complicate viral infections, the frequency and impact of mixed viral-bacterial infections has not been well studied.

Methods. Adults hospitalized with respiratory illness during 3 winters underwent comprehensive viral and bacterial testing. This assessment was augmented by measuring the serum level of procalcitonin (PCT) as a marker of bacterial infection. Mixed viral-bacterial infection was defined as a positive viral test result plus a positive bacterial assay result or a serum PCT level of ≥0.25 ng/mL on admission or day 2 of hospitalization.

Results. Of 842 hospitalizations (771 patients) evaluated, 348 (41%) had evidence of viral infection. A total of 212 hospitalizations (61%) involved patients with viral infection alone. Of the remaining 136 hospitalizations (39%) involving viral infection, results of bacterial tests were positive in 64 (18%), and PCT analysis identified bacterial infection in an additional 72 (21%). Subjects hospitalized with mixed viral-bacterial infections were older and more commonly received a diagnosis of pneumonia. Over 90% of hospitalizations in both groups involved subjects who received antibiotics. Notably, 4 of 10 deaths among subjects hospitalized with viral infection alone were secondary to complications of Clostridium difficile colitis.

Conclusions. Bacterial coinfection is associated with approximately 40% of viral respiratory tract infections requiring hospitalization. Patients with positive results of viral tests should be carefully evaluated for concomitant bacterial infection. Early empirical antibiotic therapy for patients with an unstable condition is appropriate but is not without risk.

Keywords. virus; bacterial infection; procalcitonin; pneumonia.
bacterial pneumonia and seasonal viral respiratory tract infection have been reported, there are few specific data on the risk of bacterial complications of seasonal influenza and other virus infections [1, 10, 11]. The study of bacterial lung infection has been hampered by the lack of specific and sensitive tests for invasive disease. Results of blood cultures are infrequently positive, and sputum may be contaminated by upper airway tract secretions, leading to overdiagnosis of infection [12]. In most cases, clinical, laboratory, and radiographic findings do not reliably distinguish viral from bacterial infections [13]. Newer tests such as urinary antigen analysis and polymerase chain reaction (PCR) can augment traditional microbiologic testing but are not available for all organisms. Thus, clinicians continue to struggle with ruling out bacterial respiratory tract infection in patients with viral infection, and antibiotics are almost universally used in hospitalized patients [6].

Recently, serum biomarkers such as procalcitonin (PCT) have been evaluated as surrogate indicators of bacterial infection. PCT, a calcitonin precursor normally produced in neuroendocrine cells of the thyroid and lung, is secreted by cells throughout the body in response to bacterial infections [14]. Serum PCT levels of <0.25 ng/mL are uncommon with invasive bacterial disease, and PCT determinations have been used as a guide to antibiotic therapy in patients with respiratory tract illnesses, including community-acquired pneumonia (CAP) and acute exacerbation of chronic obstructive pulmonary disease (COPD), without an increased frequency of adverse outcomes [15].

We sought to more accurately define the incidence and impact of bacterial coinfection in patients hospitalized with documented viral infection, using a panel of bacteria-specific diagnostic tests augmented by measurement of the serum PCT level.

METHODS

Patient Population
The study was performed at Rochester General Hospital in Rochester, New York. Adults aged ≥21 years admitted through the emergency department with diagnoses compatible with acute respiratory tract infection were recruited from 1 November through 30 May during 3 winters (2008–2011). Patients were screened within 24 hours of hospitalization, excluding those given antibiotics prior to admission or with immunosuppression, cavitary lung disease, or witnessed aspiration. Informed consent was obtained from subjects or their legal guardians. The study was approved by the University of Rochester and Rochester General Hospital institutional review boards.

Illness Evaluation
At enrollment, demographic, clinical, and laboratory information was collected. To provide uniformity, a primary clinical admitting diagnosis was assigned by a pulmonary specialist after examination of each subject and review of laboratory and radiographic findings. All subjects underwent testing for bacterial pathogens, including blood culture, sputum culture and Gram stain, Streptococcus pneumoniae urine antigen and pneumococcal serologic testing, and PCR of sputum and nose and throat swab specimens for Mycoplasma pneumoniae and Chlamydia pneumoniae. Sputum was induced with normal saline if subjects were unable to expectorate a sample that was considered adequate on the basis of standard criteria. Nose and throat swab and sputum specimens were tested for viruses by reverse transcription PCR (RT-PCR), and sera were collected on admission and 4–6 weeks later for viral and pneumococcal serologic testing. Serum was also collected on hospital day 2 for PCT measurement.

Laboratory Methods
Standard Microbiological Testing
Blood cultures, sputum Gram stain and culture, influenza virus antigen testing, and viral cultures were performed by the Rochester General Hospital clinical laboratory, and results were available to clinicians for patient care. Sputum samples were plated on blood, chocolate, and MacConkey agar. Legionella testing (by sputum culture and urinary antigen assay) was performed at the discretion of the treating physician. Single blood cultures positive for organisms consistent with skin flora (ie, coagulase-negative staphylococcus, corynebacterium, α hemolytic streptococci, and Propionibacterium acnes) were considered contaminants. Sputum cultures were only considered positive if more than a rare pathogenic bacteria grew from an adequate sample with the exception of Legionella.

S. pneumoniae Serologic Analysis
Pneumococcal surface protein A antigens covering families 1 and 2, obtained from the University of Alabama Bacterial Respiratory Pathogen Reference Laboratory, were used in an enzyme immunoassay [16]. A ≥4-fold rise in titer was considered evidence of infection.

Urine Antigen Testing for S. pneumoniae
Urine samples were assayed for pneumococcal antigen, using the Binax NOW urine assay (Binax, Scarborough, ME).

PCT Level
PCT levels were measured by resolved amplified cryptate emission technology (Kryptor PCT, Brahms, Henningsdorf, Germany). The functional sensitivity of the assay is 0.06 ng/mL (mean normal level [±SD], 0.033 ± 0.003 ng/mL) [17].

Viral Serologic Analysis
Immunoglobulin G titers in acute- and convalescent-phase serum specimens were determined using established methods for influenza A and B viruses, respiratory syncytial virus,
human metapneumovirus, parainfluenza types 1–3, and human coronaviruses 229E and OC43 [18]. A ≥4-fold rise in the viral specific immunoglobulin G level was considered evidence of infection.

**Real-Time PCR Analysis**

Assays for respiratory syncytial virus, human metapneumovirus, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* were performed using published methods [19–21]. Human rhinovirus assays were performed on the basis of methods published by Lu et al, with the following modification of the forward primer (5'–CYGCCZGGTGTY-3') [22]. Primers and probes for other viruses were as follows: influenza A virus (Matrix gene), influenza B virus (NS1 gene), human coronaviruses 229E and OC43 (polymerase gene), and parainfluenza viruses 1–3 (nucleocapsid gene). Sequences will be supplied on request.

**Definitions**

**Virus Infection Alone**

Virus infection alone was defined as nose and throat swab samples or a sputum sample positive for any virus by one of the following assays: (1) RT-PCR (for all viruses), (2) a rapid influenza antigen test, or (3) serologic analysis (for all viruses, with exception of those detected during illness coinciding with influenza vaccination). Additional criteria involved negative results of all tests for bacteria and serum PCT values of <0.25 ng/mL on admission and day 2.

**Bacterial Infection Alone**

Bacterial infection alone was defined on the basis of negative results of viral diagnostic tests and any of the following: (1) a positive blood culture result, (2) a culture of an adequate sputum sample that was positive for a respiratory pathogen, (3) a urinary antigen test positive for *S. pneumoniae* or *Legionella pneumophila*, (4) a serologic assay positive for pneumococci, (5) a PCR assay positive for *M. pneumoniae* or *C. pneumoniae*, or (6) a serum PCT level of ≥0.25 ng on admission or hospital day 2.

**Mixed Viral-Bacterial Infection**

A mixed viral-bacterial infection met the definitions for bacterial infection and viral infection.

**Statistical Methods**

Continuous variables were compared using the nonparametric Wilcoxon test, and categorical variables were compared using the Fisher exact test. Pearson correlation coefficients were used to summarize dependencies between pairs of continuous variables. For univariate analysis comparing mixed viral-bacterial infection with viral infection alone, the false-discovery rate was used to account for multiple comparisons [23]. Multiple logistic regression analysis was used to model the outcome (mixed viral-bacterial infection vs viral infection alone) as a function of a subset of candidate predictors, including age of ≥65 years, KATZ functional score, symptoms for ≥7 days, temperature of ≥38°C, pulse rate, systolic blood pressure of ≥100 beats/min, CURB-65 score, oxygen saturation level of ≥85%, peripheral white blood cell count (WBC) of ≥12,000 cells/mL, anion gap, log blood urea nitrogen level, sex, diabetes mellitus, congestive heart failure, COPD, chronic renal failure, active smoking, steroid use, influenza vaccination, clinical admission diagnoses (pneumonia, acute exacerbation of COPD, bronchitis, congestive heart failure, asthma, viral infection/influenza, or other diagnosis), nasal congestion, sputum production, confusion, wheezing, rales, positive viral PCR findings, and radiographic findings (ie, no acute disease or infiltrate). Variables not included because of missing values included pneumococcal vaccination status, percentage of neutrophils or band forms in peripheral blood, and basal metabolic index.

**RESULTS**

During the 3-year study period, 2217 hospitalizations with appropriate admission diagnoses were screened. Hospitalizations were excluded for the following reasons: prior antibiotic use (in 354), immunosuppression (in 178), witnessed aspiration (in 26), and follow up not possible (in 71); 54 hospitalizations were excluded for other reasons. Of the 1534 hospitalizations eligible for inclusion, 368 involved patients who were not able to give consent, and 324 involved patients who refused to participate. Thus, 842 hospitalizations involving 771 patients who consented to participate were included in the study (Figure 1). A microbiologic diagnosis was made in 447 (53%) of 842 hospitalizations, of which 99 (12%) involved bacterial infection alone and 348 (41%) had evidence of viral infection. Of those involving viral infection, 212 (61%) had viral infection alone, 64 (18%) had evidence of mixed viral-bacterial infection on the basis of specific bacterial testing, and 72 (21%) were identified on the basis of an elevated serum PCT level. This report will focus on the 348 hospitalizations with documented viral infection (Table 1).

Viral diagnosis was made on the basis of RT-PCR findings for 74% of hospitalizations and on the basis of serologic tests alone for the remaining 26% (Table 1). Influenza A virus was the most common virus and accounted for 10% of hospitalizations, followed by respiratory syncytial virus (7%) and human coronavirus OC43 (7%). Influenza B virus was the least frequent virus detected (0.8%). Thirty-eight hospitalizations (5%) were associated with multiple viruses. The primary clinical diagnoses associated with viral infection were acute exacerbation of COPD (in 26% of hospitalizations), pneumonia (in 21%), acute bronchitis (in 18%), and asthma exacerbation (in 18%). The clinical admission diagnoses were similar for most pathogens, although the rate of pneumonia was lowest for human
rhinovirus (in 10% of hospitalizations) and highest for human metapneumovirus (in 31%) and human coronavirus OC43 (in 30%). There were no significant differences in the rates of mixed viral-bacterial infection by viral pathogen, including 2009 pandemic A(H1N1) (bacterial co-infection rate was 35%).

For the 64 hospitalizations involving mixed viral-bacterial infections in which specific bacterial pathogens were documented, diagnosis was confirmed with blood culture (in 7 hospitalizations), sputum culture (in 35), pneumococcal urinary antigen testing (in 15), and pneumococcal serologic testing (in 19). Atypical bacteria were rarely identified (M. pneumoniae [in 2 hospitalizations] and C. pneumoniae [in 0]) during the first 2 years, and therefore testing was discontinued in the third year. S. pneumoniae accounted for 35 of 64 bacterial diagnoses (55%; Figure 2).

Of the 348 hospitalizations involving viral infection, 344 (99%) had either an admission or day 2 PCT measurement, and 317 (91%) had both values available. Correlation between day 1 and 2 PCT levels was high (R = .90; P = .0001). Overall, 105 of the 344 hospitalizations (31%) with at least 1 PCT measurement involved patients with levels of \( \geq 0.25 \) ng/mL (Table 1). On the basis of a positive bacterial test result or a PCT level of \( \geq 0.25 \) ng/mL on admission or day 2, 136 of 348 hospitalizations (39%) involving viral illnesses had evidence of mixed viral-bacterial infection (Table 1). Of these, 33 involved both positive results of bacterial tests and elevated PCT levels, 31 involved only positive results of bacterial tests, and 72 involved only elevated PCT levels. Of note, despite vigorous attempts to collect adequate sputum in a timely fashion, we were frequently unable to procure adequate sputum within 6 hours.
of antibiotic administration. Thus, in 69% of the hospitalizations with bacterial infection defined on the basis of PCT level alone, the negative results of sputum cultures were considered unreliable, compared with 51% for the group as a whole.

Hospitalizations associated with elevated PCT levels with or without positive results of bacterial tests involved patients who were similar with respect to age, rate of pneumonia, physical examination findings, and severity of illness score. In contrast, hospitalizations associated with low PCT values and positive bacterial test results involved patients who were younger, had lower severity of illness scores, and were less likely to receive a diagnosis of pneumonia (19% vs 44%; \(P = .02\)) and more likely to receive a diagnosis of asthma or COPD exacerbations (55% vs 26%; \(P = .006\)) as compared to those associated with elevated PCT values.

Clinical and laboratory variables were compared according to bacterial test positivity (Table 2). Not surprisingly, hospitalizations associated with positive blood culture results involved patients with higher severity of illness scores and abnormal findings of more laboratory tests, compared with those associated with positive results of other bacterial tests or those associated with no positive bacterial test results. No consistent differences between the groups were noted with respect to admission diagnoses or radiologic findings. Bacteremic hospitalizations involved a significantly greater percentage of PCT measurements of >0.25 ng/mL, compared with those involving no positive results of bacterial tests (86% vs 25%; \(P = .002\)). Of note, the single hospitalization involving a bacteremic subject with a low PCT level yielded a clinical diagnosis of bronchitis and 1 blood culture positive for multiple organisms (enterococci, Staphylococcus aureus, and coagulase-negative staphylococci), raising the possibility of blood culture contamination. In addition, median PCT values were higher for groups with positive bacterial test results as compared to those with no positive bacterial test results (bacteremia, \(P = .001\); urine antigen testing, \(P = .001\); pneumococcal serologic testing, \(P = .001\); and sputum culture alone, \(P = .055\)).

We compared subject and illness characteristics among hospitalizations involving viral infection alone to those involving mixed viral-bacterial infections, using the combination of a positive microbiologic test and/or serum PCT level of >0.25 ng/mL to define bacterial infection. A number of clinical features were significantly different by univariate analysis, as shown in
Table 3. Among hospitalizations associated with mixed viral-bacterial infections, subjects were older, had higher rates of chronic renal failure, more commonly received diagnoses of pneumonia, and less commonly received diagnoses of acute exacerbation of COPD and asthma. These subjects also had significantly lower systolic blood pressures, as well as significantly higher mean pulse rates, peripheral white blood cell counts, band forms, anion gaps, and blood urea nitrogen levels, although there was substantial overlap in these values. Multivariate analysis shown in Table 4 indicates that the factors that were mostly strongly predictive of mixed viral-bacterial infection \( (P < .01) \) were peripheral white blood cell count of >12,000 cells/mL (odds ratio [OR], 3.8), anion gap (OR, 1.2 per unit change), COPD (OR, 2.9), chronic renal failure (OR, 10.7), and infiltrate on chest radiograph (OR, 2.5).

Although severity of illness scores (CURB-65) were significantly higher among hospitalizations involving mixed viral-bacterial infection, rates of intensive care use, length of stay, and in-hospital mortality were not significantly different between the 2 groups (Table 5). At 1-month of follow-up, patients hospitalized with mixed viral-bacterial infection continued to require a higher level of medical care more frequently than those hospitalized without bacterial infections, but by 3 months outcomes of the 2 groups were similar.
For 90% of hospitalizations deemed to involve viral infection alone, patients were treated with antibiotics, as were patients in 92% of those judged to involve mixed viral-bacterial infection (Table 5), although patients hospitalized with bacterial infection were treated longer than those hospitalized with viral infection alone (mean treatment duration [±SD], 6.2 ± 9.0 vs 4.2 ± 4.6; false-discovery rate = .04). Potential antibiotic-related adverse events were significantly more common in the mixed viral-bacterial group (74 [54%], compared with 71 [33%] for viral infection alone; false-discovery rate = .002). Notably, 4 of 10 deaths among patients hospitalized with viral infection alone were secondary to complications of Clostridium difficile colitis.

Table 3 continued.

| Characteristic | Missing Value | Viral Alone (n = 212) | Mixed Viral-Bacterial (n = 136) | FDR a |
|----------------|---------------|-----------------------|---------------------------------|-------|
| BUN level, mg/dL | 3             | 18.5 ± 12.2           | 24.9 ± 15.4                     | <0.0001 |
| Viral PCR positive | 159 (75)     | 96 (71)               |                                 | 0.48 |
| Radiographic finding |             |                       |                                 |      |
| No acute disease | 1             | 121 (57)              | 49 (36)                         | 0.0005 |
| Infiltrate      | 1             | 55 (26)               | 69 (51)                         | <0.0001 |

Data are no. or no. (%) of hospitalizations or mean ± SD.

Abbreviations: BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; PCR, polymerase chain reaction; SaO2, oxygen saturation; WBC, white blood cell.

a The false-discovery rate (FDR), accounting for all 39 univariate tests, was used to compare variables. Unadjusted P values were smaller.

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Table 4. Multivariate Analysis of Factors Predictive of Mixed Viral-Bacterial Infections

| Covariate                                    | Odds Ratio (95% CI) | P     |
|----------------------------------------------|---------------------|-------|
| SaO2 level < 85%                             | 3.5 (1.3–9.9)       | .02   |
| WBC count ≥12.0 × 10^3 cells/µL              | 3.8 (2.1–7.1)       | <.0001|
| Pulse rate 10 beats/min                      | 1.2 (1.0–1.4)       | .04   |
| Anion gap                                    | 1.2 (1.1–1.3)       | .003  |
| COPD                                         | 2.9 (1.4–5.7)       | .003  |
| Chronic renal failure                        | 10.7 (2.0–58.1)     | .006  |
| Pneumonia admission diagnosis                | 4.3 (1.0–19.2)      | .05   |
| COPD admission diagnosis                     | 1.0 (2.4–4.4)       | 1.0   |
| Bronchitis admission diagnosis               | 1.5 (3.6–6.7)       | 0.4   |
| Asthma admission diagnosis                   | 1.9 (4.9–1.1)       | 0.4   |
| Viral infection/influenza admission diagnosis| 4.6 (9.23–5.7)      | 0.7   |
| Other admission diagnosis                    | 7.81 (8.72–71)      | 0.7   |
| Rales on examination                         | 1.9 (1.0–3.6)       | 0.04  |
| Infiltrate on chest radiograph               | 2.5 (1.3–4.9)       | 0.007 |

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SaO2, oxygen saturation; WBC, white blood cell.
bacterial infections with non–influenza viruses are similar to those observed with influenza. The high rate of mixed viral-bacterial infection identified in our study reflects the use of the serum biomarker PCT to augment comprehensive bacterial testing. In most previous studies reporting bacterial complications of viral infection, the bacterial testing was neither comprehensive nor systematic and frequently was left to the discretion of the clinician caring for the patient [26–28].

Although a number of clinical and laboratory variables were associated with mixed bacterial-viral infections, the absolute differences in individual variables from hospitalizations involving viral infection alone were small and unlikely to be helpful for patient management. Nevertheless, in our study, subjects hospitalized with mixed bacterial-viral infections were more ill than those hospitalized with viral infection alone, and administration of early appropriate antibiotics to these patients is important. However, it is also noteworthy that 61% of hospitalizations involving viral infection had no evidence of bacterial infection. Most of these individuals had normal chest radiograph findings and were hemodynamically stable, yet 90% received a course of antibiotic treatment. Four deaths due to complications from *C. difficile* colitis occurred in this group. Once considered a nuisance, *C. difficile* colitis has now evolved into a deadly syndrome with high mortality rates and relapse rates of 20%–30% [29]. These data highlight the critical need for better methods to safely reduce unnecessary use of antibiotics.

Recent European studies suggest that PCT-guided algorithms are a reasonable alternative to traditional microbiology-guided antibiotic therapy [15]. In 6 trials involving >2500 subjects with CAP or acute exacerbation of COPD who were randomly assigned to receive standard care or PCT-guided antibiotic treatment, there were no discernable adverse outcomes, and antibiotic use was significantly decreased, especially in those with non-pneumonic respiratory tract infections. In our study, serum PCT levels of ≥0.25 ng/mL correlated with radiographic pneumonia and higher severity of illness scores, which has been previously noted and is consistent with PCT level as a surrogate for invasive bacterial infection [30]. In addition, higher mean PCT levels were noted in patients who received a diagnosis of bacterial infections by a variety of methods, including blood and sputum cultures as well as pneumococcal urine antigen and serologic testing, suggesting that elevated PCT levels should heighten a clinician’s suspicion for bacterial infection. However, PCT levels may not correlate as well with less invasive bacterial infections, such as bronchitis and acute exacerbation of COPD, and thus in some patients a low PCT level may not rule out the presence of bacterial infection [31, 32]. Although issues of bacterial colonization in this population complicate interpretation, examination of the sputum may continue to be important in patients with severe underlying lung disease.

This study has a number of limitations. First, our results are only applicable to adults, and the rates of mixed bacterial-viral infection

**DISCUSSION**

Our study is the largest published prospective assessment of bacterial coinfection in patients with viral respiratory disease requiring hospitalization. Using comprehensive bacterial testing plus the serum biomarker PCT to define bacterial infection, our data indicate that nearly 40% of viral-associated hospitalizations have evidence of concomitant bacterial infection. Recent studies of 2009 pandemic influenza (A)H1N1 showed overall rates of bacterial coinfection of 20%–24% among critically ill children and adults and up to 50% among those with fatal illness [24, 25]. Much less is known regarding the bacterial complications for other viral respiratory tract infections, particularly those in adults. Our data indicates that rates and types of
infections may be quite different in children. In addition, our results may not be applicable to all adults admitted with respiratory tract infections, since most illnesses in our study were not severe, as reflected by the low mortality rate. The inability to obtain consent from some of the most critically ill patients may have underestimated the rate of mixed viral-bacterial infections. Also, despite vigorous attempts to collect adequate respiratory samples in a timely fashion, we were successful in only 51% of hospitalizations, also leading to underestimates of bacterial infection. Conversely, it is also possible that bacterial infection based on results of sputum cultures overestimates the incidence of infection, as it is often not possible to distinguish chronic colonization from infection even with adequate samples. Last, the presence of viral RNA may not always be causally associated with the illness leading to hospitalization. Prolonged viral detection following respiratory tract infection due to rhinovirus and other viruses can be seen, particularly when using sensitive molecular diagnostic tests.

In conclusion, bacterial coinfection is associated with approximately 40% of serious respiratory viral infections in adults requiring hospitalization. Patients with positive results of viral tests should be carefully evaluated for concomitant bacterial infection, and it is prudent to initiate early empirical antibiotic therapy for patients with severe viral illness or definitive radiographic pneumonia. At the present time, establishing a specific bacterial diagnosis on the basis of traditional methods remains difficult, and better bacterial diagnostic tests are needed. Future studies are needed to develop treatment algorithms that use combinations of biomarkers and clinical parameters to accurately predict patients at low risk for bacterial infection in whom antibiotics may be safely discontinued.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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