Mixed Community-acquired Lower Respiratory Tract Infections

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Although mixed infections are known to be clinically relevant in conditions such as nosocomial pneumonia and ventilator-related pneumonia, it is increasingly recognized that a substantial number of community-acquired lower respiratory tract infections may also be attributed to more than one pathogenic organism. A better definition of the true incidence of mixed infections in community-acquired lower respiratory tract infections is partly derived from recent advances in available diagnostic methods (eg, molecular biology). Two points still must be determined: whether the presence of a mixed infection is associated with altered outcomes and whether empirical antibiotic selection should be modified to account for potential polymicrobial infections.

Introduction

In lower respiratory tract infections (LRTIs), it is assumed that a single causative agent is responsible for a specific infection, although etiologic studies indicate that multiple organisms may be found in a substantial number of cases. Polymicrobial infections are a relevant cause of hospital-acquired pneumonia, involved in 40% to 60% of cases [1]. However, mixed infections are increasingly reported in community-acquired infections of the lower airways, which is of great interest because the presence of a polymicrobial infection could be associated with a more complex clinical course or may require modifications in empirical antibiotic selection strategies.

Mixed infections may result from various combinations of viruses, bacteria, fungi, and parasites interacting in several ways [2•]. The best-studied double pathogen interactions are mixed viral–bacterial infections. Longitudinal epidemiologic studies suggest an association between viral and bacterial respiratory infections with peak incidence of seasonal viral infections appearing either immediately preceding or concurrently with bacterial infections [3]. Moreover, clinical symptoms tend to be more severe and prolonged when bacterial superinfections complicate initial viral infections. Much of the excess mortality associated with influenza pandemics is the result of superimposed bacterial pneumonia [4••]. Animal models indicate that compared to uninfected mice, virally infected animals subsequently exposed to bacteria exhibit higher bacterial titers in the lung and greater systematic bacterial spread [5]. Viruses impair mucociliary transport efficiency and upregulate receptors for bacterial adherence [6]. Inflammatory cell infiltration after dual infection is much greater than after either viral or bacterial infection alone and may contribute to lung tissue damage [5–7].

Atypical bacteria (*Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*) are found collectively in approximately 25% of pneumonia cases, and individually in 5% to 10% of chronic obstructive pulmonary disease (COPD) exacerbations. Specifically, up to 60% of pneumonia cases with detection of *C. pneumoniae* are mixed infections [8], 33% to 64% of *M. pneumoniae*, and 54% to 63% of *Legionella* community-acquired pneumonia (CAP) cases reveal additive pathogens [9].

Analysis of LRTI studies shows wide variations in the frequency of mixed infections. These variations may be related to differences in studied populations (associated with age or other risk factors), geographic area, and the presence of intercurrent epidemics. Results may also be biased by the use or non-use of specific samples and microbiologic methods, or primary attention devoted to particular agents (eg, viruses or intracellular bacteria).

For this review, we performed a computer-based literature search using the U.S. National Library of Medicine PubMed search engine. Keywords used were "etiology," "lower respiratory tract infections," "community-acquired pneumonia," "mixed infections," "polymicrobial infections," and "COPD exacerbations." Articles published in or after 2002 were considered.

Mixed Community-acquired Pneumonia in Children

Esposito et al. [10] conducted a study on 196 children 2 to 5 years old with pneumonia. Serology and polymerase chain reaction (PCR) were employed for identification of *M. pneumoniae* and *C. pneumoniae* infections, and serology alone for *Streptococcus pneumoniae*. Etiologic diagnosis was reached in 110 of the 196 hospitalized patients, and evidence of a mixed infection was found in 26 patients (13.3% overall, 23.6% of patients with causal diagnosis). Sixteen cases were due to mixed *S. pneumoniae* plus atypical bacterial pneumonia, whereas the other 10 cases were mixed atypical bacteria infections.

Laundy et al. [11] conducted a 6-month prospective study on influenza A community-acquired pneumonia in infants and young children ages 1 to 5 years. In addition to standard culture methods on blood and respiratory samples, PCR and indirect immunofluorescence were applied for respiratory viruses (respiratory syncytial virus [RSV], influenza A and B viruses, parainfluenza virus, and adenovirus), whereas *C. pneumoniae* was detected serologically. An etiologic agent was identified in 25 of 51 patients (49%), with influenza A and RSV as most common causal agents. Mixed viral–bacterial infections were found in 10% of the 51 patients, and in 20% of those with etiologic diagnosis. Mixed infections were associated with higher C-reactive protein values than in patients with single causal agents for pneumonia.

A Finnish group recently re-evaluated a subgroup of 153 of 245 CAP patients up to 5 years old who had been analyzed in a previous study so as to determine the clinical response to antibiotic therapy [12]. Respiratory viruses were sought through culture and immunologic antigen and antibody assays. PCR was employed for rhinovirus identification. Serology for *S. pneumoniae*, *M. pneumoniae* and *C. pneumoniae* was performed. In 127 of 153 patients, an etiologic agent was identified, with 44 mixed infection cases (28.8% of total pneumonia cases, 34.6% of cases with identified pathogens). The most common combinations were *S. pneumoniae* plus either rhinovirus or RSV. Interestingly, approximately half the patients with a treatment failure had evidence of a mixed infection, and among patients who were still febrile 48 hours after antibiotic therapy initiation, 75% had a viral infection, usually with a concomitant bacterial infection.

In a study of older children ages 5 to 14 years, 75 hospitalized young patients with CAP underwent microbiologic workup including PCR-based detection of respiratory viruses and atypical bacteria [13]. In addition, serologic testing for *C. pneumoniae*, *M. pneumoniae*, *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* was performed. A causal microorganism was identified in 58 of 75 patients (65%). Infection with more than one pathogen was present in 26 patients (34.7% of total cases, 44.8% of cases with etiologic diagnosis). Of these, 21 cases were mixed viral–bacterial infections, four were double viral infections, and one was a double bacterial infection. The most common mixed infection was rhinovirus plus *M. pneumoniae* pneumonia.

Other studies have evaluated the etiology of CAP across the whole age spectrum of childhood. Over a 15-month study period, Michelow et al. [14] recruited 154 patients ages 2 months to 17 years who were hospitalized for CAP. Bacterial cultures were performed on blood samples and invasive respiratory samples, and culture and direct fluorescent antibody detection were applied for common respiratory viruses on nasopharyngeal and oropharyngeal swabs. Serologic testing was carried out for *M. pneumoniae*, *C. pneumoniae*, and respiratory viruses. CAP etiology was determined in 122 of 154 patients (79%). A mixed viral–bacterial infection was found in 23% of cases, multiple bacterial etiology in 3%, and a multiple viral infection in 3%. Patient stratification by age group revealed that the incidence of mixed viral–bacterial infections was greatest in the 2- to 5-year-old age group and subsequently declined in children over 5 years old. No association between mixed etiology and specific clinical, laboratory, or radiographic presentation was found.

A recent study evaluated the incidence of *M. pneumoniae* pneumonia in children in primary healthcare in Finland [15]. Over a 12-month study period, 201 cases of pneumonia in children up to 15 years old were analyzed. All patients underwent serologic testing for typical and atypical bacteria. Evidence of *M. pneumoniae* infection was found in 61 patients (30%). Thirty-one of these cases (51%) were mixed infections. Specifically, coinfections with *S. pneumoniae* and *C. pneumoniae* were present in over 30% and 15%, respectively, of mycoplasmal CAP cases. Mixed *M. pneumoniae* plus *C. pneumoniae* cases were detected only in children older than 10 years of age.

A recent 12-month study conducted in southeast Asia of 209 hospitalized CAP children up to 18 years old investigated the effects of mixed chlamydial infections on clinical outcome [16]. Overall, leading pathogens were *S. pneumoniae*, *M. pneumoniae*, and viruses, with a very high rate of observed coinfections (40.7%). Specifically, *C. pneumoniae* was identified in 26 of 209 cases of pneumonia, and 21 of these patients (80.7%) had coexistent infection with other pathogens, mainly *S. pneumoniae* and *M. pneumoniae*. Clinical and laboratory signs associated with mixed chlamydial infection were tachypnea, wheezing, and higher C-reactive protein levels on admission. Of note, 11 of the 12 patients with *C. pneumoniae* pneumonia who required respiratory therapy and both patients who required admission to a pediatric intensive care unit had a mixed infection, suggesting that chlamydial coinfections may be associated with worse clinical course.

Mixed Community-acquired Pneumonia in Adults

A Swedish study on primary care patients with pneumonia treated at home identified 82 patients with CAP over a

3-year study period [17]. Patients underwent sputum culture testing, serology for atypical bacteria, respiratory viruses, and *S. pneumoniae*. A polymicrobial infection was found in 21 patients (25.6% of total cases, 35% of the 60 cases with causal diagnosis). Most common associations involved *S. pneumoniae* or *H. influenzae* with an atypical bacteria or a virus. Beovic et al. [18] analyzed 109 Slovenian patients with mild CAP. Bacterial cultures, paired serology for atypical bacteria, and urinary antigen determinations for *S. pneumoniae* and *L. pneumophila* were performed. A mixed infection was present in nine patients (8.3% of total cases, 13.2% of the 68 cases with etiologic diagnosis). Conversely, a recent study examined the etiology of CAP in ambulatory patients tested with blood and sputum culture, and serology for *M. pneumoniae* and *C. pneumoniae* found evidence of dual atypical bacterial pneumonia in only 2.1% of total cases and 4.5% of etiologically determined cases among 507 patients [19].

Van der Eerden et al. [20] recruited 262 patients hospitalized for CAP in the Netherlands over a 2-year study period. Patients were evaluated with blood and sputum culture, serology for atypical bacteria and respiratory viruses, Legionella urinary antigen detection, pneumococcal antigen detection in urine, and noninvasive and invasive respiratory samples. The overall diagnostic yield was 158 of 262 patients (60%). A mixed infection, consisting in a combination of bacterial pathogen plus an atypical bacterial pathogen or a respiratory virus, was present in 17 (6%) patients.

Outside Europe, several studies recently evaluated the etiology of CAP patients (mostly hospitalized) in the Far East [21–24]. Evidence of a mixed infection was found in 7.2% to 25.9% of total cases, and in 13% to 35.5% of cases with etiologic diagnosis. The highest number of mixed infections was recorded in a recent Japanese study on 232 inpatients and outpatients with CAP. In addition to standard culture and serologic methods, the researchers employed PCR techniques for the diagnosis of atypical bacteria and leading respiratory viruses [23]. In a study conducted in Thailand comparing ambulatory and hospitalized CAP cases in 245 patients, rather surprisingly, mixed infection was over twice as common in outpatients (17.6%) compared to hospitalized patients (8.6%) with etiologic diagnosis [21]. *C. pneumoniae* was the most common coinfecting agent in this study. Huang et al. [24] studied 389 patients over 2 years old (36.2% treated as outpatients) over a 2-year period and identified *H. influenzae* plus either *M. pneumoniae* or *C. pneumoniae* as the most common combinations among the 28 of 155 (18%) patients with pneumonia etiologic diagnosis.

Use of PCR techniques for the diagnosis of important respiratory pathogens (atypical bacteria and viruses) may increase the overall diagnostic yield in patients with pneumonia, both as single and multiple infections, as addressed in a recent work by Templeton et al. [25]. The authors enrolled 105 outpatients and hospitalized cases of CAP who underwent conventional diagnostic techniques and additional use of multiplex real-time PCR for atypical bacteria and respiratory viruses. The use of molecular biology techniques increased overall microbial detection from 49.5% to 76% of patients, a figure which rose to almost 90% in elderly patients and patients with severe CAP. Specifically, compared to conventional diagnostic methods, the addition of PCR increased detection of mixed infections from 3 of 105 to 28 of 105 (28/80 [35%] among those with etiologic diagnosis). Half of these mixed infections were in patients with pneumonia severity index class IV or V CAP. Mixed infection in patients with severe CAP was significantly associated with the presence of human rhinovirus and human coronavirus.

Only two recent studies have specifically investigated the characteristics of mixed etiology CAP in adult patients [26•,27••]. Over a 2-year study period, Gutiérrez et al. [26•] prospectively evaluated 493 consecutive patients with CAP, 73% of whom were admitted to the hospital. Researchers performed sputum and blood gram-stain and cultures, urinary antigen detection for *L. pneumophila* and *S. pneumoniae*, and serology for atypical bacteria and respiratory viruses. A single pathogen was identified in 222 (45%) cases, and two or more pathogens were identified in 5.7% patients with microbiologic diagnosis. A wide variability of pathogen combinations existed among mixed infections, the most common being a bacterial organism plus an atypical pathogen and a combination of two pyogenic bacteria.

Across all age groups in both hospitalized and outpatient cases, *S. pneumoniae* was involved in almost two thirds of mixed infections. In this study, 17.8% of pneumococcal infections were mixed. Patients with mixed infections did not differ significantly from patients with monomicrobial infections in terms of major clinical and epidemiologic characteristics. However, polymicrobial infections more commonly presented a predefined underlying medical condition (eg, diabetes, chronic lung or heart disease, chronic liver disease, chronic renal failure, cancer immunosuppression, dementia malnutrition), and dementia as an underlying disease. Interestingly, patients with mixed infections were less likely to have diabetes as an underlying disease. This finding is in contrast with a study analyzing CAP outcome in patients with diabetes that found an identical rate of mixed infections among diabetic and nondiabetic patients (9%) [28].

In the study by Gutiérrez et al. [26•] patients with mixed infections tended to have higher pneumonia severity scores, rates of hospital admissions, frequencies of pleural effusions and hypoxemia, and mortality rates than those with monobacterial infections. However, none of these associations reached statistical significance. When a series of predefined complications (ie, pleural effusion, empyema, atelectasis, mechanical ventilation, and septic shock) were grouped as a composite variable, a higher number of patients with mixed infections presented this

variable compared to those with single-agent infections, and this difference reached statistical significance. Bacteremia was recorded in 2 of 28 mixed infections.

The largest study to date specifically studying mixed infections was carried out in Spain by de Roux et al. [27••] on 1511 patients hospitalized for CAP over a 5-year period. In addition to traditional culture (blood, noninvasive and invasive respiratory samples) and serology for atypical bacteria and respiratory viruses, these authors employed antigen detection tests for *L. pneumophila* and *S. pneumoniae*. With an overall diagnostic yield in 610 (40%) cases, the rate of mixed infections was once again rather low (5.4% of total CAP cases, 13.4% of etiologically determined cases). At least one pyogenic pathogen was involved in 58 of 82 (70%) patients with mixed infection, whereas 35% of polymicrobial cases had an atypical bacteria or virus. *S. pneumoniae* was present in 54% of mixed infections. Conversely, 16% of pneumococcal infections were mixed, and the figure rose to 25% if only cases with paired serology were included. Approximately two thirds of mixed pneumococcal infections were associated with a respiratory virus, mainly influenza. The most common polymicrobial combination overall was *S. pneumoniae* plus *H. influenzae*.

No differences in clinical, radiographic, or laboratory data on admission were found between single and multiple pathogen cases of pneumonia. The two groups showed no differences in underlying diseases. Although mortality rates were similar between the two groups, patients with mixed infections had a significantly greater propensity to develop shock, and borderline significance for greater requirement for intensive care unit admission. These findings suggest that infections involving multiple pathogens may present a greater propensity to spread from the lung, thus causing systemic compromise. Other studies have indeed associated mixed infections with more severe pneumonia [25,29,30], although this association did not translate into greater mortality rates. A possible explanation is that associated factors such as age and comorbidities are responsible for the increased severity allocation rather than the presence of multiple pathogens. Recent etiologic studies carried out in patients with severe CAP identify mixed infections in 6.8% [31] to 9.4% [32] of cases with etiologic diagnosis.

Mixed Community-acquired Pneumonia in the Elderly

The incidence of pneumonia increases with age. Aspiration of microorganisms from oropharyngeal secretions and dental plaques is a major cause of pneumonia in the elderly, both in the community and those who are hospitalized. In a study using molecular genotyping techniques, El-Solh et al. [33] demonstrated that pathogens recovered from bronchoalveolar lavage fluid of patients matched microorganisms recovered from dental plaques in roughly 60% of cases. The etiology of aspiration pneumonia has traditionally been attributed to a combination of different anaerobic pathogens including *Bacteroides*, *Peptostreptococcus*, *Prevotella*, and *Fusobacterium* spp. However, recent studies have questioned these findings.

El-Solh et al. [34] examined 95 elderly patients with severe aspiration pneumonia. A polymicrobial infection was present in 12 (22%) of the 54 patients in whom a microbiologic diagnosis was determined. Gram-negative enteric bacilli were the most commonly encountered pathogens, associated with anaerobic bacteria. A recent study compared the features of community-acquired versus institutionalized aspiration pneumonia in elderly patients [35]. The authors found that decreased levels of consciousness were more commonly associated with community-acquired aspiration pneumonia, whereas many patients with aspiration pneumonia in continuing care facilities presented with dysphagia, usually related to neurologic disorders.

The largest study on CAP in the elderly was conducted prospectively in Spain over 78 months [36]. It recruited almost 1500 elderly patients, and analyzed two subgroups: patients older than 80 years old and patients younger than 80 years old. Authors performed sputum and blood cultures; urine antigen tests for pneumococcus and *Legionella*; and serology for *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. Serology for leading respiratory viruses was available only for the first years of the study. In patients under 80 years of age, a definitive etiologic diagnosis was reached in 409 cases, 37 of which were mixed infections (9%). In CAP patients over 80 years old, multiple pathogens were recorded in 5 of 66 cases with definitive causal diagnosis (7.6%). Aspiration pneumonia was present in 5% of the younger age group and in 10% of the very elderly cases.

Mixed Infections in COPD Exacerbations

The role of infective agents in COPD exacerbations has been debated. Earlier microbiologic studies, which focused primarily on bacterial etiology, have identified mixed infections in 29% of bacterial exacerbations [37] and in 33% of severe exacerbations requiring mechanical ventilation [38]. More recently, a bacterial polymicrobial etiology was identified in 6 of 86 (7%) patients with COPD exacerbations [39]. Over the last 5 years, attention has been drawn to the viral etiology of exacerbations. Seemungal et al. [40] used serology, culture, and PCR for viral and atypical bacterial identification in 83 patients who showed 321 exacerbations during a 12-month study period. Rhinovirus was the most commonly identified agent (23.3% of exacerbations), and 11 exacerbations (6.5%) showed evidence of coinfection with rhinovirus plus another respiratory virus (mainly RSV and influenza).

A later German study, based once again primarily on viral detection, examined 85 COPD patients during an

exacerbation [41]. All patients underwent nested reverse-transcriptase PCR for leading respiratory viruses. A virus was identified in 48 of 85 patients (56%). In 10 of 48 cases (21%) multiple viruses were identified. These viruses were found more commonly on sputum samples than in nasal samples, suggesting an etiologic role in the exacerbations.

Although most previous studies have focused primarily on viral or bacterial etiologies of COPD exacerbations, few have gathered data on both. Bandi et al. [42] examined 35 exacerbations associated with sputum isolation of nontypeable *H. influenzae*. In addition, strain-specific immune responses to new *H. influenzae* strains were also evaluated during the exacerbation, providing further proof for the etiologic role of this bacterium. The patients were studied for evidence of viral infection using viral culture, serology, and PCR-based assays. In 16 of 35 (45.7%) *H. influenzae*–associated exacerbations, evidence of an acute viral infection was also found. Rhinovirus, parainfluenza type 3, and influenza A were the most commonly isolated viruses. Dual viral infections were identified in two subjects. Furthermore, a positive strain-specific immune response to nontypeable *H. influenzae* was found in three patients with evidence of viral infection.

In a recent study on COPD exacerbations requiring mechanical ventilation, Cameron et al. [43], recruited 105 patients presenting with 107 exacerbation episodes. Immunofluorescence, culture, and PCR for viruses were employed. Paired virus and atypical bacteria serology was performed. Blood, sputum, and endotracheal aspirates were cultured for bacteria. Evidence of a polymicrobial infection was found in 13 of 76 (29%) infective episodes. Viruses were involved in 11 of 13 multiple pathogen infections (mostly influenza, parainfluenza, and RSV). Pyogenic bacteria were present in nine of 13 mixed infections (seven with viruses, two with atypical bacteria), whereas *Chlamydia* was present in three of 13. Wilkinson et al. [44••] recently performed an interesting study evaluating the interaction between bacterial and rhinoviral infections in COPD exacerbations. The authors prospectively studied 56 COPD exacerbations, obtaining samples for bacterial culture, performing PCR for rhinovirus, testing lung function, and analyzing airway inflammation through cytokine level determinations. A bacterial pathogen, most often *H. influenzae,* was identified in 69.6% of exacerbations, and rhinovirus was found in 19.6%. The fall in forced expiratory volume in one second (FEV_1) associated with exacerbations presenting with colds (taken as a marker of viral infection) and presence of a lower airway bacterial pathogen was greater than with a cold alone or a bacterial pathogen alone (-20.3%, -3.63%, and -3.13%, respectively). Similarly, exacerbation symptoms were more severe in cases with colds and bacterial infections. Most importantly, exacerbations associated with both *H. influenzae* and rhinovirus documented infection exhibited greater bacterial load and serum interleukin-6 than those without both pathogens. The study suggests a synergistic effect of viral and bacterial infections in COPD exacerbations, because systemic inflammation, exacerbation symptoms, and lung function changes were all more severe when both agents were present.

In an editorial commenting on this paper, Sethi [45] reasons that COPD patients may present a peculiar mode of viral–bacterial interaction. Traditionally, it is thought that in healthy, normally sterile lower airways, viruses (notably influenza) may cause epithelial damage, thus predisposing to the development of secondary bacterial infections such as pneumonia. Conversely, the lower airways in COPD are very often chronically colonized by bacterial pathogens. Colonization is by no means a passive process, but is accompanied by chronic airway inflammation that may facilitate subsequent viral infections. COPD may therefore represent an alternative paradigm, whereby long-standing bacterial infection facilitates viral infections.

Papi et al. [46••] observed 64 COPD patients with severe exacerbations, tested with sputum culture and PCR for atypical bacteria and respiratory viruses. In this study, 78% of exacerbations were associated with respiratory virus and/or bacterial infection. The presence of coinfection with both viruses and bacteria was found in 25% of exacerbations. These patients had more severe functional impairment and longer hospitalization.

Conclusions

Mixed community-acquired lower respiratory tract infections are more common than previously recognized. In the setting of pneumonia, polymicrobial infections are present at all ages, although there may be important differences. In children, mixed viral–bacterial infections are highly prevalent, with an increase in atypical bacterial coinfections after school-age that appear to persist into adulthood. On one hand, elderly patients are at risk for gram-negative and anaerobic polymicrobial aspiration pneumonia, and on the other hand are more prone to bacterial superinfections following influenza infection. Presentation characteristics do not help distinguish between monomicrobial and polymicrobial infections, although the latter tend to be associated with greater underlying diseases and may be linked to a more severe clinical course.

S. pneumoniae is the leading pathogen in the etiology of CAP. It is important to bear in mind that 16% to 45% of pneumococcal infections are mixed, generally involving an atypical bacteria or a virus. The potential importance of mixed infections is highlighted by recent retrospective studies showing that combined antimicrobial therapy including a macrolide given empirically may reduce mortality associated with bacteremic pneumococcal pneumonia [47]. Recent treatment recommendations have incorporated the idea that atypical pathogen infection should be considered in all patient groups, sometimes in the form of mixed infection.

The observed rate of mixed viral–bacterial infections in pneumonia may also lead to new treatment considerations. In individual patients during influenza epidemics, use of rapid detection techniques such as real-time PCR may allow the use of effective neuraminidase inhibitors such as oseltamivir and zanamivir within 36 to 48 hours of symptom onset, thus reducing the emergence of secondary bacterial complications (including pneumonia) by up to 50% [48]. On a larger scale, the known association between influenza and excess mortality for pneumonia underscores the importance of widespread influenza vaccination in eligible patients, as this has been shown to reduce pneumonia hospitalizations and deaths [49].

Important data in exacerbated COPD patients suggest that the presence of a mixed viral-bacterial etiology may be associated with more severe disease and greater inflammation. In this disease, chronic airway bacterial colonization may facilitate subsequent viral infection, rather than vice versa. A need clearly exists for more research work to investigate this association further.

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