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EDITORIAL COMMENTARY

Coinfections in Hospitalized Children With Community-Acquired Pneumonia: What Does This Mean for the Clinician?

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(See the Major Article by Nolan et al, on pages 179–88.)

Community-acquired pneumonia (CAP) is one of the most common infections in children admitted to the hospital [1]. The leading pathogens causing CAP in hospitalized children are respiratory viruses, including influenza virus, respiratory syncytial virus (RSV), and human metapneumovirus; bacterial pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus*; and the atypical bacterium *Mycoplasma pneumoniae*. In the prospective Etiology of Pneumonia in the Community (EPIC) study, investigators from the Centers for Disease Control and Prevention, along with those from children's hospitals in Nashville, Memphis, and Salt Lake City, determined the etiology of radiographically proven CAP in >2200 hospitalized children from January 2010 through June 2012 [2]. An etiology was proven or implied for 81% of children, using standard microbiologic culture, serologic techniques, and molecular testing. Viral etiologies were primarily implied on the basis of findings from molecular testing of nasopharyngeal specimens, which may or may not reflect the true pathogen causing the lower respiratory tract infection, especially cases due to human rhinovirus. As expected, viral etiologies were most common, with ≥1 virus detected in 66% of patients, whereas typical-bacterial pathogens (primarily *S. pneumoniae*) were identified in 8%. Evidence of *M. pneumoniae* infection was found in 8% of patients. Multiple pathogens were detected in 26%, both bacteria and viruses in 7%, and multiple viruses in almost 20%, particularly in children <5 years of age.

The interactions of viruses and bacteria in the pathogenesis of both local and invasive respiratory tract infections have been studied for many years. The mechanisms by which preceding influenza virus infections lead to a secondary bacterial infection with *S. aureus* or *S. pneumoniae* have been of particular interest [3–5]. In this issue of *The Journal of Infectious Diseases*, Nolan et al [6] examined the EPIC database to further understand the impact of copathogens on the clinical manifestations and outcome of CAP in hospitalized children. As noted above, 26% of children (576 of 2219) had coinfections detected. Of great interest were the 99 children who had ≥1 virus and ≥1 typical bacterium identified. RSV and human rhinovirus were the viruses found most often as single pathogens and were also the viruses most commonly found as copathogens with other viruses or bacteria. *S. pneumoniae* was codetected with RSV in 11 patients, parainfluenza virus and coronavirus in 8 each, human metapneumovirus in 7, and influenza virus in 4. *S. aureus* was identified with ≥1 virus in 13 children. *M. pneumoniae* was a copathogen with ≥1 virus, most commonly human rhinovirus (n = 18), influenza virus (n = 6), and RSV (n = 4), in 48 children. However, demographic and clinical characteristics of children with CAP, including age, underlying conditions, duration of illness prior to admission, prevalence of cough, prevalence of fever, prevalence of chest retractions, and chest radiography findings at admission, were not different between children with typical bacteria alone and those with viral and typical bacterial copathogens or between children with *M. pneumoniae* alone and those with *M. pneumoniae* and viral copathogens. Not unexpectedly, children with typical bacteria alone or with viral and typical bacterial copathogens were more likely than children with viruses alone to have a consolidation pattern on their admission chest radiograph or a parapneumonic effusion sometime during hospitalization. There was 1 difference noted for virus-virus coinfections as compared to single-virus infections, with higher rates of supplemental oxygen use in the first 24 hours of hospitalization in the group with virus-virus copathogens. In an earlier study from Dallas, clinical characteristics (pneumonia was most common) were not significantly different among 129 children with invasive pneumococcal disease (IPD) with (n = 28) or without (n = 101) a viral coinfection [5].

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From a diagnostic standpoint, it is important to know whether the biomarkers associated with CAP in children are modified in infection caused by viral and typical bacterial copathogens as compared to infection due to a typical bacterium alone. In this study, total white blood cell counts and percentages of neutrophils and band forms were almost identical in the group with typical bacteria alone as compared to the group with viral and typical bacterial copathogens, as well as in the group with atypical bacteria (predominantly *M. pneumoniae*) alone as compared to the group with viral and atypical bacterial copathogens. In another study using the EPIC database and stored residual sera, procalcitonin concentrations were determined in a subset of patients (532 of 1397 [38%]) enrolled at Salt Lake City and Nashville sites [7]. Procalcitonin levels were similar for patients with CAP due to typical bacteria alone (n = 17; median, 2.98 ng/mL; interquartile range [IQR], 0.93–12.48 ng/mL), compared with the group with viral and typical bacterial copathogens (n = 37; median, 6.64 ng/mL; IQR, 0.80–26.63 ng/mL). However, the authors cautioned that, with typical bacteria detected in only 54 children, their study could not exclude the possibility that viral coinfections could lower procalcitonin concentrations in pediatric CAP due to bacterial-viral coinfection. Viral coinfection also did not change the procalcitonin levels in children with CAP caused by atypical bacteria (n = 24; median, 0.13 ng/mL; IQR, 0.07–0.50 ng/mL), compared with those with CAP due to atypical bacterial monoinfection (n = 58; median, 0.09 ng/mL; IQR, 0.06–0.21 ng/mL). In the Dallas IPD study, no significant differences were noted for total white blood cell count, percentage of bands, erythrocyte sedimentation rate, or C-reactive protein level between 28 children with viral coinfections and 54 children with negative viral test results [5]. So at least from the published studies to date, a viral coinfection does not appear to significantly affect biomarkers in children with bacterial infection, especially IPD.

Recently, a novel assay has been described that uses a combination of biomarkers (tumor necrosis factor–related apoptosis-inducing ligand, interferon γ–induced protein 10, and C-reactive protein) to distinguish bacterial from viral infections [8, 9]. The cutoffs for this test include a value above which a bacterial infection is likely, and this includes mixed bacterial and viral infections. In these combined studies, <200 children with lower respiratory tract infections were included. Thus, it would be important to evaluate this new assay in a large prospective study designed like the EPIC study, to ensure that a viral copathogen does not significantly affect the test result in hospitalized children with bacterial CAP.

With respect to clinical outcomes, no differences in supplemental oxygen use in the first 24 hours, intensive care admission, invasive mechanical ventilation use, or hospital length of stay were found between children infected with typical bacteria alone as compared to those coinfected with viruses and typical bacteria. Other studies have reported similar results. In the Dallas IPD study, the proportion of children requiring intensive care unit admission or intubation also did not differ between the group with and the group without a viral coinfection, although the authors noted a more severe clinical course in patients with adenovirus coinfection, of whom 2 of 6 died [5]. In an 8-center pediatric pneumococcal surveillance study, 377 patients with pneumococcal pneumonia requiring hospitalization were identified [10]. Of children tested for respiratory viruses, 31 of 46 (67%) with a viral copathogen, compared with 92 of 137 (67%) with negative viral test results, had pneumococcal pneumonia complicated by a large pleural effusion, loculated pleural fluid, parapneumonic empyema, necrotizing pneumonia, or lung abscess.

In the pediatric EPIC study, *S. aureus* was identified in only 22 children; in about half, ≥1 viral copathogen was detected. Because of these small numbers, the authors could not specifically assess the impact of viral coinfection on the outcome of *S. aureus* pneumonia, which is often associated with necrotizing pneumonia and can be fatal [11, 12]. In a retrospective study from 1 children's hospital of 117 children with *S. aureus* pneumonia acquired predominantly in the community between August 2001 and April 2009, viral copathogens were detected in 18 of 68 patients tested (26%); parainfluenza virus (n = 6), influenza virus (n = 5), and rhinovirus (n = 4) were the most common viral copathogens [13]. The children with viral copathogens were more likely to develop respiratory failure and have longer intensive care unit stays than the children without a viral copathogen.

For physicians managing hospitalized children, perhaps the most important finding in the study by Nolan et al is that a viral copathogen is present in a large percentage of children with CAP caused by typical bacteria, such as *S. pneumoniae* and *S. aureus*, or by atypical bacteria, such as *M. pneumoniae*. This was also noted in another study on IPD from Dallas, occurring from January 2011 to December 2014, during which 44% of patients underwent viral testing; 60% of those tested were positive for viruses [14]. Thus, detection of a virus in a hospitalized child with CAP by one of the widely available molecular tests for detecting multiple respiratory viruses does not exclude the presence of infection due to typical or atypical bacteria. Nolan et al noted that the clinical manifestations, laboratory and radiographic findings, and outcomes of CAP among children with viral and typical bacterial coinfection were similar to those for children infected with typical bacteria alone and more severe than for patients infected with viruses alone. Furthermore, the analysis by Stockman et al [7] reported significantly higher concentrations of procalcitonin in children with CAP due to viral and typical

bacterial coinfection as compared to those with CAP due to viruses alone. Finally, Nolan et al observed no differences in clinical or laboratory findings between children with CAP due to atypical bacteria alone, compared with those with viral and atypical bacterial coinfection. Thus, the interpretation of rapid molecular tests positive for respiratory viruses in hospitalized children with CAP and the decision about whether to initiate antibiotic treatment still require considerable clinical judgment.

Notes

Potential conflicts of interest. S. L. K. reports participating in an investigator-initiated and collaborative multicenter pneumococcal surveillance study; participating in an investigator-initiated study of ceftaroline in pediatric osteomyelitis, supported by Allergan; serving as an advisor for a US study of the ImmunoExpert assay, sponsored by MeMed Diagnostics; and receiving honoraria for international lectures on PCV13, supported by Pfizer.

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