Clinical Infectious Diseases

EDITORIAL COMMENTARY

Is There an Association Between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and *Streptococcus pneumoniae?*

Leigh M. Howard

Department of Pediatrics, Division of Pediatric Infectious Diseases and the Vanderbilt Vaccine Research Program, Vanderbilt University Medical Center, Nashville, Tennessee, USA

(See the Major Article by Amin-Chowdhury on pages e65–e75.)

Keywords. *Streptococcus pneumoniae*; invasive pneumococcal disease; SARS-CoV-2; COVID-19; viral-bacterial interactions.

Synergistic interactions between respiratory viruses and *Streptococcus pneumoniae* (pneumococcus) have been extensively investigated. Although impactful viral–pneumococcal interactions have been described with common respiratory viruses, including human rhinovirus and respiratory syncytial virus [1–4], these interactions have been most widely studied with influenza and pneumococcus, in part, prompted by the dramatically increased mortality due to secondary pneumococcal pneumonia during the 1918 influenza A/H1N1 pandemic [5–12]. It has been hypothesized that respiratory viral infections create favorable conditions in the nasopharyngeal mucosa for colonizing pneumococci to invade, leading to mucosal disease such as pneumonia and otitis media, as well as invasive pneumococcal diseases (IPD), including bacteremia and meningitis. Several mechanisms for viral facilitation of bacterial colonization have been proposed. Respiratory viruses may alter the integrity of the respiratory epithelia, enhancing conditions for bacterial adherence and translocation, as well as inducing factors required for bacterial adherence and by influencing immunological defenses of the host epithelium [13]. Epidemiological and ecological observations suggest that coinfection with respiratory viruses such as influenza, human rhinovirus, and respiratory syncytial virus is common in children with pneumococcal pneumonia and IPD [14, 15], and rates of IPD temporally correlate with periods of high activity of these viruses [4, 16, 17].

Despite the widespread global effects of the coronavirus disease 2019 (COVID-19) pandemic, until now little has been reported regarding the potential bacterial, specifically, pneumococcal interactions with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus associated with COVID-19. Several earlier studies that used various methods and definitions to identify bacterial coinfections in patients hospitalized with COVID-19 have reported coinfection frequencies that ranged from 3.5% for confirmed community-onset bacterial infection [18] to 28% among patients admitted to the intensive care unit, when detections of respiratory bacteria in multiplex panels from upper respiratory samples were included in the definition [19–21]. In one study, while the overall frequency of secondary bacterial infection, defined as bacterial detection in a bronchoalveolar lavage, bronchial, or sputum samples, was 8.5%, 35% of patients with "critical" disease were found to have secondary bacterial infection compared with only 4% of those with moderate and 9% with "severe" disease [20]. Another study that reported secondary bacterial infection (defined as positive blood or lower respiratory tract culture) frequencies of 15% overall, but frequencies of 50% of nonsurvivors compared with 1% of survivors of COVID-19 [21]. These important studies, however, did not examine the role of coinfection with specific bacteria, such as pneumococci, in COVID-19–associated clinical course and outcomes.

In this issue of *Clinical Infectious Diseases*, Amin-Chowdhury [22] and coauthors present one of the first examinations of potential interactions that may occur in the setting of pneumococcal and SARS-CoV-2 coinfection. The authors provide evidence to support a potentially synergistic relationship between SARS-CoV-2 and pneumococci, with markedly higher mortality associated with coinfection and/or secondary infection occurring within 28 days of the initial infection than with either infection alone. The authors used national data from the well-established Public Health England (PHE) surveillance system, capturing clinical and microbiological data on all cases of IPD, defined as pneumococcal detection from a

Received 27 November 2020; editorial decision 30 November 2020; published online 3 December 2020.

Correspondence: Leigh Meredith Howard, Vanderbilt University Medical Center, CCC-5317 MCN, 1161 21st Ave South Nashville, TN (leigh.howard@vumc.org).

Clinical Infectious Diseases® 2021;72(5):e76–8

DOI: 10.1093/cid/ciaa1812

sterile site, since 2000. This surveillance platform also linked SARS-CoV-2 infections identified in PHE laboratories and national hospitals, the main source of SARS-CoV-2 testing during the study period, and IPD during the pandemic period. They found that rates of IPD were significantly lower in 2019/2020 than in 2018/2019 across all age groups, with the greatest reductions observed during March 2020 to June 2020, coinciding with the sharp rise in SARS-CoV-2 detections and implementation of lockdown measures to reduce SARS-CoV-2 transmission. Simultaneous SARS-CoV-2 infections and cases of IPD were uncommon and occurred primarily in the early period of the pandemic. Even fewer cases of secondary infection occurred within 3–28 days of diagnosis of the first infection, with IPD preceding SARS-CoV-2 infection in all but 1 of the identified cases. However, despite being uncommon, after adjustment for age, pneumococcal serotype, and gender, simultaneous IPD/COVID-19 coinfections were associated with more than 7-fold higher odds and secondary COVID-19 following IPD was associated with nearly 4-fold higher odds of death within 28 days compared with IPD alone.

Much of the existing literature focuses on the risk of secondary bacterial infections following respiratory viral infections. The unique observations presented in this manuscript, that infections appeared to occur primarily in the reverse sequence with IPD most frequently followed by COVID-19, raises interesting questions. While the premise that respiratory viral infection may predispose to secondary bacterial infection is well studied, current understanding of a potential role for colonizing respiratory bacteria in influencing the response to subsequent viral infection is very limited. The findings presented by Amin-Chowdhury and colleagues may suggest a hypothesis that infection with certain respiratory bacteria may influence the risk of infection and severe illness associated with SARS-CoV-2 infection. This is of particular interest given that while some risk factors for severe disease associated with SARS-CoV-2 infection have been identified [21], these remain incompletely described, and severe outcomes may occur even in individuals with no underlying comorbidities.

Nasopharyngeal pneumococcal colonization, which is common in children as well as in adults with close contact with children, is typically asymptomatic but represents a critical initial step preceding the development of IPD. The authors' finding that death occurred in nearly half of individuals with SARS-CoV-2 infection within the 3- to 27-day period after IPD suggests that nasopharyngeal pneumococcal carriage prior to SARS-CoV-2 exposure/infection may modify risk of severe COVID-19 illness. While data are limited, an earlier study conducted by our group among young children in rural Peru suggests that increases in the density of colonizing nasopharyngeal pneumococci during asymptomatic periods is associated with the subsequent development of acute respiratory illness within 4 weeks. The illnesses that followed increases in pneumococcal density were typically mild, brief, and associated with detection of a respiratory virus, and the great majority resolved without antibiotics [23, 24]. This suggests a contributing role, but not necessarily a primary etiological role, for colonizing pneumococci in the pathogenesis of these mild "cold"-like respiratory illnesses that have typically been considered virus-associated. Further study is needed to determine whether a similar contributing role exists for preexisting nasopharyngeal pneumococcal colonization in influencing the symptom course of SARS-CoV-2 infection.

While compelling, the findings presented by Amin-Chowdhury et al should be interpreted in the context of several important considerations. The authors acknowledge that very little community testing was performed during the initial phase of the SARS-CoV-2 pandemic, resulting in the majority of testing occurring in symptomatic patients who presented to the hospital for care. Therefore, that IPD occurred in the 3- to 27-day period following mild SARS-CoV-2 infection that was managed in the outpatient setting would have remained undetected as such. Additionally, it is not possible to determine the sequence of infection in coinfection cases. Thus, while few secondary cases of IPD were observed, the incidence of secondary IPD cases following COVID-19 may be underestimated. Furthermore, a number of the SARS-CoV-2 infections were acquired during the 3- to 14-day period after IPD diagnosis among patients with a negative SARS-CoV-2 test at hospital admission, suggesting the possibility of nosocomial acquisition among this vulnerable group. Additionally, from available data, it is difficult to estimate whether coinfection with SARS-CoV-2 and pneumococci occurred at a rate that is greater than that expected by chance, given the dynamic patterns of SARS-CoV-2 circulation and detection throughout the early and later phases of the pandemic, as well as the national lockdown, which may have resulted in unpredictable transmission patterns for both pathogens differentially across specific subpopulations. Finally, while the significantly higher mortality observed in patients with coinfection or subsequent SARS-CoV-2 infection within 28 days after IPD is compelling, the authors note that most deaths occurred in the elderly and among those with multiple comorbidities. Patients who are more medically frail and/or exhibit certain comorbidities may be more likely to be exposed to and/or exhibit severe manifestations of pneumococcal and SARS-CoV-2 infection [20, 21, 25]. A more detailed understanding of this association of SARS-CoV-2 and pneumococcal infection with increased mortality could be strengthened by accounting for these potentially confounding factors in future studies.

Respiratory viral infections infect the nasal mucosa in the setting of a complex

and dynamic microbial community, and interactions that occur between respiratory viruses and nasopharyngeal bacteria may have important implications for disease pathogenesis and severity. Studies of pneumococcal infections associated with both the 1918 and the 2009 influenza pandemics as well as with other respiratory viral infections have underscored this concept. However, whether SARS-CoV-2 and pneumococcal interactions exist in the upper respiratory tract and whether these dynamic interactions may alter the course of SARS-CoV-2 and/or pneumococcal infection remain largely unexplored. The findings presented by Amin-Chowdhury and colleagues reveal new and important insights into a potential synergistic interaction between SARS-CoV-2 and pneumococcal infection, findings that may contribute improved insight into the pathogenesis of SARS-CoV-2. Future studies that use longitudinal assessments, taking into account pneumococcal colonization and density patterns before, during, and after SARS-CoV-2 infection, will further elucidate the contributions of these potential interactions to SARS-CoV-2 pathogenesis and ultimately enhance response efforts to this global threat.

Notes

Financial support. Dr. Howard is supported by the National Institutes of Health under award number 1K23AI141621.

Potential conflicts of interest. The author reports no conflicts of interest. The author has 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.

References

1. Fan RR, Howard LM, Griffin MR, et al. Nasopharyngeal pneumococcal density and evolution of acute respiratory illnesses in young children, Peru, 2009–2011. Emerg Infect Dis **2016**; 22:1996–9.
2. Howard LM, Fan R, Zhu Y, et al. Nasopharyngeal pneumococcal density is associated with viral activity but not with use of improved stoves among young Andean children. Open Forum Infect Dis **2017**; 4:ofx161.
3. Greenberg D, Givon-Lavi N, Faingelernt Y, et al. Nasopharyngeal pneumococcal carriage during childhood community-acquired alveolar pneumonia: relationship between specific serotypes and coinfecting viruses. J Infect Dis **2017**; 215:1111–6.
4. Weinberger DM, Klugman KP, Steiner CA, Simonsen L, Viboud C. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med **2015**; 12:e1001776.
5. Shrestha S, Foxman B, Weinberger DM, Steiner C, Viboud C, Rohani P. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med **2013**; 5:191ra84.
6. Diavatopoulos DA, Short KR, Price JT, et al. Influenza A virus facilitates *Streptococcus pneumoniae* transmission and disease. FASEB J **2010**; 24:1789–98.
7. Walter ND, Taylor TH, Shay DK, et al; Active Bacterial Core Surveillance Team. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis **2010**; 50:175–83.
8. McCullers JA, McAuley JL, Browall S, Iverson AR, Boyd KL, Henriques Normark B. Influenza enhances susceptibility to natural acquisition of and disease due to *Streptococcus pneumoniae* in ferrets. J Infect Dis **2010**; 202:1287–95.
9. Siegel SJ, Roche AM, Weiser JN. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. Cell Host Microbe **2014**; 16:55–67.
10. Mina MJ, Klugman KP. Reply to "no clinical association of live attenuated influenza vaccine with nasal carriage of bacteria or acute otitis media": specific recommendations for future studies. mBio **2014**; 5:e01173–14.
11. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med **2005**; 118:285–91.
12. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev **2006**; 19:571–82.
13. Bosch AA, Biesbroek G, Trzcinski K, Sanders EA, Bogaert D. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog **2013**; 9:e1003057.
14. Wolter N, Tempia S, Cohen C, et al. High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia. J Infect Dis **2014**; 210: 1649–57.
15. Techasaensiri B, Techasaensiri C, Mejías A, McCracken GH Jr, Ramilo O. Viral coinfections in children with invasive pneumococcal disease. Pediatr Infect Dis J **2010**; 29:519–23.
16. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J **2011**; 30:456–61.
17. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity. Clin Infect Dis **2014**; 58:188–94.
18. Vaughn VM, Gandhi T, Petty LA, et al. Empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized with COVID-19: a multi-hospital cohort study. Clin Infect Dis **2020**; ciaa1239. doi:10.1093/cid/ciaa1239.
19. Contou D, Claudinon A, Pajot O, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care **2020**; 10:119.
20. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med **2020**; 201:1380–8.
21. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet **2020**; 395:1054–62.
22. Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the COVID-19 pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with SARS-CoV-2: prospective national cohort study, England. Clin Infect Dis. doi:10.1093/cid/ciaa1728.
23. Howard LM, Zhu Y, Griffin MR, et al. Nasopharyngeal pneumococcal density during asymptomatic respiratory virus infection and risk for subsequent acute respiratory illness. Emerg Infect Dis **2019**; 25:2040–7.
24. Budge PJ, Griffin MR, Edwards KM, et al; RESPIRA-PERU Group. A household-based study of acute viral respiratory illnesses in Andean children. Pediatr Infect Dis J **2014**; 33:443–7.
25. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax **2015**; 70:984–9.