J Pediatr (Rio J). 2013;89(5):421–423

Jornal de Pediatria
www.jped.com.br

EDITORIAL

Respiratory viral coinfection and clinical disease severity☆,☆☆

Coinfecção viral respiratória e gravidade da doença clínica

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Even though the pandemic caused by Influenza A(H1N1)pdm09 (pH1N1) infection has been extensively investigated, there are few studies that have examined the impact of viral coinfection on disease severity, and they have yielded conflicting results. In this issue of the Jornal de Pediatria, Scotta et al.[1] report on a retrospective study of 120 Brazilian children hospitalized with pH1N1 infection, which found respiratory viral coinfection to be a risk factor for respiratory failure. Consistent with this finding, Torres et al. observed that viral coinfection with respiratory syncytial virus (RSV) was associated with increased mortality in a multivariable analysis of 142 children admitted for intensive care during the first pandemic wave in Argentina.[2] In contrast, viral coinfection was infrequent and had little impact on morbidity and mortality in a sample consisting mostly of adult patients (79.3%) admitted to an intensive care unit (ICU) in Australia.[3] In a large study of children and adults conducted in North West England, coinfection with RSV or adenovirus was associated with increased risk of admission to the general ward, while influenza B increased risk of admission to ICU; however, in multivariable logistic regression models, these increases in risk were not statistically significant.[4] In the same study, coinfection with seasonal influenza A and influenza B viruses was associated with a significant increase in risk of ICU admission or death. Rhedin et al. observed no correlation between detection of additional viruses and disease severity in Swedish children hospitalized with pH1N1 infection.[5] Similarly, studies with limited sample sizes in Spain[6] and Brazil[7] found no association between respiratory viral coinfection and severity of pH1N1 infection. Meanwhile, in a study sample that included 96 (42.0%) children, Esper et al. found that rhinovirus coinfection had little impact on severity of influenza disease; in fact, such patients had a lower median clinical severity score, while the opposite was observed for non-rhinovirus coinfection.[8]

Similar to studies of pH1N1 infection, reports focusing on the relative importance of mixed viral respiratory infections generally have resulted in equally divergent findings. Some studies documented increased severity[9–11] of respiratory illness in children infected with two or more viruses compared to those with single virus infections, while some observed the opposite.[12–14] Other studies found no association of respiratory coinfections with illness severity.[15–17] These discrepant findings may be explained by several factors. They include differences in the population studied (variation in age ranges, breadth of illness severity, and proportions of subjects with comorbid conditions), geographical and seasonal differences regarding circulating respiratory viruses, method of viral detection (traditional methods, such as culture and direct immunofluorescence, *versus* molecular assays), and composition and performance characteristics of

DOI of original article:
http://dx.doi.org/10.1016/j.jped.2013.01.010

☆ Please cite this article as: Tran D. Respiratory viral coinfection and clinical disease severity. J Pediatr (Rio J). 2013;89:421–3.

☆☆ See paper by Scotta M.C. et al. in pages 444–9.

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http://dx.doi.org/10.1016/j.jped.2013.06.002

the molecular respiratory panels. The mechanisms driving disease virulence in coinfections are not clearly understood. Some authors have proposed three major groups of virus-virus interactions to explain potential mechanistic models of disease: (1) direct interactions of viral genes or gene products, (2) indirect interactions resulting from alterations in the host environment, and (3) immunological interactions.[18] In this context, it would not be surprising for different pathogenic mechanisms to be triggered by different viruses that mutually potentiate or mitigate each other's effects; thus, certain pairings of viruses may be more clinically relevant than others. Furthermore, the simultaneous detection of multiple viruses does not necessarily implicate pathogenic effect at the time of detection, especially when molecular methods are used. In some instances, detection of two viruses may represent an acute infection in the presence of viral persistence from a recent infection.[19]

The potential confounding influence of concurrent bacterial infections is another important factor that may have contributed to the conflicting results in studies examining the role of respiratory viral coinfection in the determination of disease severity due to respiratory infections, including influenza. Influenza and other respiratory viral infections are known to predispose to secondary bacterial pulmonary infection.[20] Bacterial coinfection complicates at least 2.5% of influenza cases in older individuals and those with predisposing conditions.[20] In a series of 838 critically ill children with pH1N1 infection, 22% had clinical evidence of bacterial coinfection along with positive bacterial cultures.[21] Thus, failure to account for the influence of bacterial coinfection may bias results. For example, a recent study by Chorazy et al.[13] of 346 archived respiratory specimens from children treated for acute respiratory illness at the University of Iowa Hospitals and Clinics found that children with viral coinfections were less likely than those with single virus infections to require intensive care in unadjusted analysis.[13] However, the authors observed that children with virus-bacteria coinfections were more likely to require ICU admission than those with single virus infections, even after controlling for potential confounders; they also found that virus-bacteria coinfections represented a greater proportion of virus-positive specimens than virus-virus-bacteria coinfections. Once children with virus-bacteria coinfections were excluded from the analysis, the observed odds ratio moved toward the null, suggesting that the observed association of virus-virus coinfection with better outcome can be partly explained by virus-bacteria coinfection. Besides the study by Chorazy et al.,[13] a minority of the studies cited in the present editorial either considered or adjusted for bacterial coinfection, or a proxy thereof, as a potential confounder in the analysis.[5,11,12,17] Even when such adjustments are performed, residual confounding by undetected bacterial coinfections may remain, as exemplified by Scotta et al.[1] in this issue of the Jornal de Pediatria. The authors had stipulated bacterial co-detection (defined as a positive culture for a possible pathogen in respiratory secretions, blood, or other sterile specimens) as one of the independent variables to be examined, but presented no bacterial co-detection data, presumably due to the lack of microbiologically-confirmed bacterial infection in the study cohort.

The increasing use of molecular respiratory viral panels in clinical settings underscores the importance of a fuller understanding of the impact of viral coinfection on disease severity. Future prospective longitudinal studies that include serial respiratory tract sampling, not only for virus detection but also for mechanistic experiments, will be paramount to the understanding of the clinical significance of polymicrobial acute respiratory infections, as well as viral pathogenesis. Implementation of multiplex quantitative polymerase chain reaction assays into the study design may also be a worthwhile goal, as is the precise and comprehensive identification of bacterial coinfection.

Conflicts of interest

The author declares no conflicts of interest.

References

1. Scotta MC, Mattiello R, Maróstica PJ, Jones MH, Martins LG, Fischer GB. Risk factors for need of mechanical ventilation in children with influenza A(H1N1)PDM09. J Pediatr (Rio J). 2013;89:444–9.
2. Torres SF, Iolster T, Schnitzler EJ, Farias JA, Bordogna AC, Rufach D, et al. High mortality in patients with influenza A pH1N1 2009 admitted to a pediatric intensive care unit: a predictive model of mortality. Pediatr Crit Care Med. 2012;13:e78–83.
3. Blyth CC, Webb SA, Kok J, Dwyer DE, van Hal SJ, Foo H, et al. The impact of bacterial and viral coinfection in severe influenza. Influenza Other Respi Viruses. 2013;7:168–76.
4. Goka E, Vallely P, Mutton K, Klapper P, Influenza A. viruses dual and multiple infections with other respiratory viruses and risk of hospitalisation and mortality. Influenza Other Respi Viruses. 2012 Oct 19 [Epub ahead of print].
5. Rhedin S, Hamrin J, Naucler P, Bennet R, Rotzén-Östlund M, Färnert A, et al. Respiratory viruses in hospitalized children with influenza-like illness during the H1n1 2009 pandemic in Sweden. PLoS One. 2012;7:e51491.
6. Cordero E, Perez-Romero P, Moreno A, Len O, Montejo M, Vidal E, et al. Pandemic influenza A(H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral coinfection. Clin Microbiol Infect. 2012;18:67–73.
7. Camargo C, Guatura SB, Bellei N. Respiratory viral coinfection among hospitalized patients with H1N1 2009 during the first pandemic wave in Brazil. Braz J Infect Dis. 2012;16:180–3.
8. Esper FP, Spahlinger T, Zhou L. Rate and influence of respiratory virus co-infection on pandemic (H1N1) influenza disease. J Infect. 2011;63:260–6.
9. Drews AL, Atmar RL, Glezen WP, Baxter BD, Piedra PA, Greenberg SB. Dual respiratory virus infections. Clin Infect Dis. 1997;25:1421–9.
10. Marcone DN, Ellis A, Videla C, Ekstrom J, Ricarte C, Carballal G, et al. Viral etiology of acute respiratory infections in hospitalized and outpatient children in Buenos Aires, Argentina. Pediatr Infect Dis J. 2013;32:e105–10.
11. Cilla G, Oñate E, Perez-Yarza EG, Montes M, Vicente D, Perez-Trallero E. Viruses in community-acquired pneumonia in children aged less than 3 years old: high rate of viral coinfection. J Med Virol. 2008;80:1843–9.
12. Martin ET, Kuypers J, Wald A, Englund JA. Multiple versus single virus respiratory infections: viral load and clinical disease severity in hospitalized children. Influenza Other Respi Viruses. 2012;6:71–7.
13. Chorazy ML, Lebeck MG, McCarthy TA, Richter SS, Torner JC, Gray GC. Polymicrobial acute respiratory infections in a

hospital-based pediatric population. Pediatr Infect Dis J. 2013 Jan 23 [Epub ahead of print].
14. Canducci F, Debiaggi M, Sampaolo M, Marinozzi MC, Berrè S, Terulla C, et al. Two-year prospective study of single infections and co-infections by respiratory syncytial virus and viruses identified recently in infants with acute respiratory disease. J Med Virol. 2008;80:716–23.
15. García-García ML, Calvo C, Pérez-Breña P, De Cea JM, Acosta B, Casas I. Prevalence and clinical characteristics of human metapneumovirus infections in hospitalized infants in Spain. Pediatr Pulmonol. 2006;41:863–71.
16. Peng D, Zhao D, Liu J, Wang X, Yang K, Xicheng H, et al. Multipathogen infections in hospitalized children with acute respiratory infections. Virol J. 2009;6:155.
17. De Paulis M, Gilio AE, Ferraro AA, Ferronato AE, do Sacramento PR, Botosso VF, et al. Severity of viral coinfection in hospitalized infants with respiratory syncytial virus infection. J Pediatr (Rio J). 2011;87:307–13.
18. DaPalma T, Doonan BP, Trager NM, Kasman LM. A systematic approach to virus-virus interactions. Virus Res. 2010;149:1–9.
19. Jartti T, Söderlund-Venermo M, Hedman K, Ruuskanen O, Mäkelä MJ. New molecular virus detection methods and their clinical value in lower respiratory tract infections in children. Paediatr Respir Rev. 2013;14:38–45.
20. Metersky ML, Masterton RG, Lode H, File Jr TM, Babinchak T. Epidemiology, microbiology, and treatment considerations for bacterial pneumonia complicating influenza. Int J Infect Dis. 2012;16:e321–31.
21. Randolph AG, Vaughn F, Sullivan R, Rubinson L, Thompson BT, Yoon G, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics. 2011;128:e1450–8.