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Multiplex polymerase chain reaction testing in pediatric inpatients with febrile seizures

To the Editor:

In their large retrospective study, Subramony et al[1] compared the use of antibiotics, chest radiographs, and isolation precautions for patients <18 years old, hospitalized at a tertiary referral center and tested for respiratory pathogens in the emergency department or during the first 2 hospital days during a non-multiplex polymerase chain reaction period (non-mPCR; 2349 patients) vs a multiplex polymerase chain reaction period (mPCR; 2430 patients). The authors demonstrated that patients in the mPCR group had more positive tests (42.4% vs 14.4%, $P < .01$), had received fewer days of antibiotics (4 vs 5 median antibiotic days, $P < .01$), had fewer chest radiographs performed, (59% vs 78%, $P < .01$), and were placed in isolation longer (20 vs 0 median isolation-hours, $P < .01$) compared with the non-mPCR group. In multivariable regression, patients tested with mPCR were less likely to receive antibiotics for ≥2 days (OR 0.5, 95% CI 0.5-0.6), chest radiographs at admission (OR 0.4, 95% CI 0.3-0.4), and more likely to be in isolation for ≥2 days (OR 2.4, 95% CI 2.1-2.8) compared with the non-mPCR group. The number of antibiotic days per patient days, however, was similar (75 vs 86 antibiotic days per 100 patient days; $P = .4$). Also, and of note, children in the mPCR group were older, had more complex chronic conditions, and were admitted to the intensive care unit more frequently compared with the non-mPCR group. The authors concede that their main findings may not be generalizable to different subsets of pediatric patients, and this finding is in line with the inconsistent impact of mPCR testing found in other clinical settings.[2,3]

We would like to add some specific data with regard to the use of mPCR testing in children with febrile seizures,[4] a common pediatric neurologic emergency. In our retrospective study, we evaluated the role of mPCR analysis in diagnosis of viral illness in children with febrile seizures, comparing data from a premultiplex era (2009) with a period after introduction of routine respiratory multiplex analysis (2010-2013). We also investigated whether the detection of viral pathogens by mPCR analysis translates into a significant reduction in antibiotic use. Our multiplex panel (FTD Respiratory pathogens 21; Fast-Track Diagnostics Ltd, Sliema, Malta) included the following virus detections: influenza A/H1N1; influenza B; parainfluenza type 1, 2, 3, 4; coronavirus (NL63, 229E, OC43, HKU1); human metapneumovirus (A/B); human bocavirus; rhinovirus; adenovirus; respiratory syncytial virus (A/B); parechovirus; and enterovirus. This commercial, real-time PCR assay was performed according to the manufacturer's instructions with excellent performance in a number of studies.[5]

After institutional review approval by our local ethics committee, 200 children with febrile seizures (mean age: 29.5 ± 1.4 months; 104 male) were included in this retrospective cohort study. Sites of infections were respiratory (44.5%), gastroenteritis (11%), tonsillitis (10.5%), otitis media (7.5%), urinary tract infection (1%), and vaccination-related fever (1%). In 11.5% of children, a combination of different foci was seen, and in 13% of children, no definite site of infection could be established. In 2009, microbiology testing (bacterial/fungal) was positive in 10 of 49 (20%) children compared with 74 of 151 (49%) children in 2010-2013 ($P < .01$). The number of children treated with antibiotics increased from 34.6% in 2009 to 48.3% in 2010-2013, and the rate of positive virological studies increased from 20% to 48.3% ($P < .01$). mPCR analysis confirmed viral infections in 52 of 73 cases (71.2%). The most common detected viruses (multiple entries possible) by mPCR were adenovirus (12), human bocavirus (10), enterovirus (9), rhinovirus (7), respiratory syncytial virus (7), corona virus (7), parechovirus (5), parainfluenza virus (5), and human metapneumovirus (3).

Contrary to the results from the study by Subramony et al,[1] and in line with previous other reports and meta-analysis,[2,3] routine mPCR testing did not translate into a significant reduction in the use of antibiotics in our cohort. This finding may at least in part be attributable to the specific condition of febrile seizures with the potential underlying diagnosis of meningitis/encephalitis, thus contributing to a "liberal" use of antibiotics. It remains, however, somewhat unclear why an increase in the use of antibiotics was seen in our cohort because no substantial changes in antimicrobial stewardship were implemented during this period. The noted increase in the use of diagnostics and antibiotic treatment, however, may be caused by children with more serious infections, because more uncomplicated cases (simple febrile seizure) are treated with minimal interventions, possibly in an outpatient setting.[6] Also, it is important to note that a substantial number of patients were started on antibiotics before they were admitted to the hospital.

Krause et al[7] concluded that the high sensitivity of PCR-based methods is an important contribution to the diagnostic assessment of children with respiratory tract infections, but from a clinical perspective, it still remains difficult to exclude a concomitant bacterial infection, especially in immunocompromised patients. Moreover, children can shed viral nucleic acids of specific pathogens for prolonged periods, and their detection may not be directly associated with the acute illness.

In addition, the interpretation of mPCR analysis also can be difficult when more than one virus is detected, particularly in respiratory specimens.[5] On the basis of our findings, we conclude that mPCR is useful in detecting underlying viral causes of febrile seizures, but the precise role of mPCR technique in the management of these children awaits clarification. Moreover, it will be important to assess the role, potential, and limitations of mPCR testing in well-defined subgroups of pediatric patients.

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Reply

To the Editor:

Meyer et al raise a number of interesting points regarding the use of multiplex polymerase chain reaction (mPCR) testing in patients with febrile seizures. In their letter, the authors report findings from their study on the use of antibiotics in patients with febrile seizures before and after the initiation of mPCR testing. In their analysis of 200 children with febrile seizures, they note an increase in rates of positive viral tests after initiation of mPCR, as well as an increase in patients with positive bacterial/fungal testing, which possibly could have contributed to the increase in children treated with antibiotics. Although we look forward to reviewing the complete data in a peer-reviewed manuscript, we recognize that they do highlight the need to understand the use and interpretation of mPCR results in specific populations.

In summary, we agree that although viral respiratory testing may contribute to diagnosis, it should be used in conjunction with other factors, including clinical presentation, physical examination, epidemiologic data, and other testing to determine the etiology of acute respiratory illnesses. Meyer et al highlight the need for future studies in this area among specific populations, such as patients with febrile seizures.

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