The Journal of Molecular Diagnostics, Vol. ■, No. ■, ■ 2017

the Journal of Molecular Diagnostics
jmd.amjpathol.org

Impact of Rapid Molecular Respiratory Virus Testing on Real-Time Decision Making in a Pediatric Emergency Department

Q15 Daniel T. Rogan,* Mohit S. Kochar,† Samuel Yang,† and James V. Quinn†

From the Departments of Health Research and Policy, and Emergency Medicine,† Stanford University, Stanford, California*

Accepted for publication January 25, 2017.

Address correspondence to Samuel Yang, M.D., or James V. Quinn, M.D., 300 Pasteur Dr., Rm M121, Alway Bldg. MC 5119, Stanford, CA 94305. E-mail: syang5@stanford.edu or quinnj@stanford.edu.

Acute respiratory illnesses (ARIs) are usually viral [influenza, respiratory syncytial virus (RSV)] and account for 25% of emergency department (ED) peak-season visits. Laboratory respiratory PCR testing is accurate albeit slow for ED management, whereas rapid antigen testing is inaccurate. We determined the impact of bedside influenza/RSV PCR (molecular point-of-care test; mPOCT) on pediatric ARI management. This was a prospective cohort study of consecutive pediatric patients with ED-ordered respiratory PCR test, enrolled over 9 weeks during peak flu season. On ordering PCR testing, ED physicians were interviewed to ascertain real-time diagnostic and disposition plans if given immediate influenza/RSV PCR results for the current patient. Two groups were compared: actual management and management adjusted for mPOCT results. We compared ED length of stay (LOS), tests ordered, and antibiotic/antiviral ordering. One-hundred thirty-six respiratory PCR panels were ordered, 71 by admitting team, 61 for ED management. Of 61 ED-initiated tests, physicians indicated in 39 cases (64%) that they would change patient management if bedside viral results were available. Physicians would have decreased ED LOS by 33 minutes, ordered fewer tests (18%; $P < 0.001$) with average patient charge savings of $669, fewer antibiotics among discharged patients (17%; $P = 0.043$), and increased appropriate antiviral use (13%; $P = 0.023$). Rapid bedside ARI mPOCT PCR has the potential to decrease ED LOS, reduce diagnostic tests and patient charges, and increase appropriate use of antibiotics and antiviral agents. *(J Mol Diagn 2017, ■: 1–8; http://dx.doi.org/10.1016/j.jmoldx.2017.01.009)* Q2

Q3 During the winter months, fever and respiratory infection symptoms make up to 25% of all emergency department (ED) visits.[1] Acute respiratory illness (ARI) is a leading cause of hospitalization for young children, contributing to 10.4% of all deaths in children younger than 5 years.[2,3] ARI has a large spectrum of disease, ranging from mild upper respiratory tract problems to severe lower respiratory infections (eg, bronchiolitis and pneumonia) that can be associated with significant rates of morbidity and mortality. Although most ARIs are viral in cause with influenza (A and B) and respiratory syncytial virus (RSV) being most common, symptoms are often nonspecific, therefore making causative diagnosis based on clinical presentation unreliable.[4] Q4 Furthermore, the Centers for Disease Control and Prevention currently recommend administration of antiviral agents within 48 hours of symptom onset for children younger than 2 years of age or young immunocompromised children who are at high risk of influenza-related complications.[5]

There is a need and desire to improve diagnosis and management in the ED setting.[6] Current criterion standard laboratory tests based on traditional real-time PCR, which may require up to several hours for turnaround time, are too slow to affect ED management.[7] Without a confirmed viral

Supported by NIH TL1 Clinical Research Training Program of the Stanford Clinical and Translational Science Award to Spectrum grant TR 001084 (D.T.R.). Q1

S.Y. and J.V.Q. contributed equally as senior authors.

Disclosures: Support for study coordinators and investigator time provided to S.Y. and J.V.Q. by Roche Molecular Systems, Inc. through an investigator-initiated RFA.

http://dx.doi.org/10.1016/j.jmoldx.2017.01.009

diagnosis, ED physicians may resort to precautionary patient management strategies that result in antibiotic overuse and antiviral misuse, additional diagnostic testing, and unnecessary hospitalizations requiring isolation beds.[8,9] These conservative measures promote antibiotic and antiviral resistance in the population and increase overall health system expenditures. In particular they contribute to prolonged ED wait times, length of stay (LOS), and overcrowding. Further, prior studies have shown that reducing testing turnaround times and initiating diagnostic testing earlier during ED triage reduces ED LOS.[10,11] Antigen tests can provide results between 30 and 150 minutes with near-patient testing capability, but they have unacceptable sensitivity as low as 10% for influenza and RSV in certain studies.[12,13] As a result, studies have shown antigen testing has limited impact on ED patient management.[14]

Recent technologic advances in molecular diagnostics have enabled the development of fully automated PCR platforms with point-of-care (POC) capability to detect influenza A and B and RSV with >95% sensitivity and specificity and turnaround time as fast as 20 minutes.[15–18] These emerging rapid molecular POC tests (mPOCTs) are designed to be performed at the bedside by minimally trained personnel. Before the clinical availability of these tests with Food and Drug Administration (FDA) clearance for waived status under Clinical Laboratory Improvement Amendments (CLIA), we performed a study to determine the impact and potential value of rapid influenza and RSV PCR results on physician decision making in a pediatric ED during peak ARI season (*https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K153544*; *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Detail.cfm?ID=39763&NoClia=1*, last accessed January 10, 2017).

Materials and Methods

Study Design

This was a prospective observational study with real-time interviews of physicians during active patient management in the ED, when a PCR test for respiratory viruses was ordered.

Study Setting

The study occurred in the pediatric ED of an academic medical center during peak ARI season. It involved consecutive pediatric patients younger than 18 years of age who had a respiratory virus PCR panel by nasopharyngeal swab in the Pediatric Emergency Department at Stanford University Medical Center during the 9-week study period from January 10, 2016, to March 13, 2016.

Study Protocol

During the study period patients were identified by a real-time electronic notification system developed to identify patients in real time for clinical studies.[19] No post hoc convenience surveys were administered at any time. The electronic notification was set according to the order coming from the pediatric ED in a patient younger than 18 months for a respiratory virus PCR panel. This set up a real-time notification to the on-call research coordinator who then contacted the ordering attending ED physician to conduct a brief survey relating to patient management within minutes of the respiratory panel order being placed. Given the real-time nature of the electronic notifications and immediate subsequent interviews, interviews were possible at any time of day throughout the study period.

At the time of the survey, while patients were still being actively managed in the ED, physicians were informed that the viral PCR as an mPOCT would have results within 20 minutes of a nasopharyngeal swab. Further, physicians were informed the test would present individually positive or negative viral presence results for RSV, influenza A, and influenza B (influenza A and B collectively referred to as influenza). This theoretical mPOCT was considered to have the same diagnostic accuracy as the commercially available standard respiratory panel PCR test used at the institution (Respiratory Virus Panel XT8; GenMark, Carlsbad, CA), Q5 albeit only testing for RSV and influenza A/B.[15] Physicians were asked hypothetically how their patient management would change if the mPOCT results were available imminently, including whether fewer diagnostic testing [urinalysis (UA), blood draw, or chest X-ray (CXR)] would have been pursued if a source of fever was identified (Supplemental Figure S1). Potential changes in antibiotic use and oseltamivir use and changes in disposition were also surveyed. Physicians' *a priori* proposed plans according to potential mPOCT results were retroactively aligned with test results from the hospital laboratory standard 14-virus PCR test; this allowed determination of individual theoretical management plans that the physician would have followed if test results had been known in the ED compared with actual ED management performed in the absence of test result information.

Hospital Laboratory Respiratory Viral Detection

Per standard practice at our institution, ED nasopharyngeal swabs for viral testing are transported to an off-site institutional facility for processing by fully trained laboratory staff. Viral DNA/RNA is extracted with the EZ1 Virus Mini Kit version 2.0 (Qiagen, Hilden, Germany), and virus is detected via Respiratory Virus Panel XT8 (GenMark). Total turnaround time is between 8 and 24 hours, factoring in transport and handling, assay time (7 hours), and allowance for batch testing (two to five times daily, seasonally depending on staffing and volume concerns). No changes in institutional standard of practice for ordering or processing respiratory virus panels were made during the conduction of this study.

FLA 5.4.0 DTD ■ JMDI587_proof ■ 21 March 2017 ■ 8:33 pm ■ EO: 2017_15