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Short report

Effect of target-enriched multiplex polymerase chain reaction on patient outcomes and costs during the 2013–14 influenza season

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SUMMARY

The US Centers for Disease Control and Prevention recommends the initial use of rapid antigen influenza diagnostic test (RIDT) for the detection of influenza A (H1N1-09). Nasopharyngeal samples were tested from 246 patients for H1N1-09 using target-enriched multiplex polymerase chain reaction (TEM-PCR), of which 163 were additionally tested via RIDT. RIDTs had a sensitivity of 18.7% compared with TEM-PCR as the reference standard. Patients with false-negative RIDTs were withheld from 111 days of oseltamivir and 65 days of isolation. Patients negative for H1N1 via TEM-PCR had antiviral therapy immediately stopped, thereby evading 408 days of oseltamivir and 315 days of unnecessary isolation. This cost avoidance saved US$208,982.

Introduction

Since its pandemic in 2009, influenza virus A/H1N1 2009 (H1N1-09) has remained a potent pathogen and was the dominant virus detected during the 2013–14 influenza season, causing 28,322 infections throughout the USA [1]. The US Centers for Disease Control and Prevention (CDC) recognizes polymerase chain reaction (PCR) and viral culture as the gold standard assays for the diagnosis of H1N1, but recommends the rapid antigen influenza diagnostic test (RIDT) as the first-line diagnostic for patients exhibiting influenza symptoms [2]. Despite widespread use, RIDTs have high false-negative rates with sensitivities ranging from 10% to 80% [1,3]. Most RIDT protocols require high virus concentrations, which may not be readily available during sampling. Moreover, since adults tend to shed less influenza virus than children, low sensitivity in adults may be due to sample selection effects [3]. To examine

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the possible limitations of RIDTs, we assessed the clinical and economic impact of the Target Enriched Multiplex–PCR Respiratory Panel (TEM-PCR™; Diatherix Laboratories, LLC, Huntsville, AL, USA) for the diagnosis of H1N1 and its positive effects on isolation practices, on use of neuraminidase inhibitors, and on reduction of antimicrobial coverage.

Methods

Patient sample description

Retrospective chart review revealed that 163 symptomatic patients from Huntsville Hospital (Huntsville, AL, USA) were tested for H1N1 by both RIDT and TEM-PCR as detailed below. After comparing test results of these patients, Huntsville Hospital moved away from the RIDT and adopted the TEM-PCR Respiratory Panel for routine use. An additional 83 patients were tested by TEM-PCR only and results were analysed. All 246 patients were inpatients and exhibited severe flu-like symptoms associated with pneumonia, high fever, and respiratory distress. TEM-PCR nasopharyngeal specimens were collected from December 2013 to February 2014 using a nylon flocked swab and transported to a reference laboratory in a tube filled with 1 mL of modified liquid Amies media which are components of the eSwab™ liquid-based collection and transport system (Copan Diagnostics, Murrieta, CA, USA). TEM-PCR results were reported to hospital physicians one day after sample receipt.

RIDT

BinaxNow® (Alere, Waltham, MA, USA), was used at the point-of-care following the manufacturer's protocol.

This study was approved by the Huntsville Hospital Institutional Review Committee in December 2013.

Target-enriched multiplex PCR

The TEM-PCR Respiratory Panel contains 35 genetic targets for the simultaneous detection of 27 respiratory pathogens with high diagnostic sensitivity and specificity, including two targets encoding haemagglutinin 1 (H109C) and neuraminidase 1 (N109B) indicative of H1N1-09. Further details on TEM-PCR are available from previous literature [4].

Calculations of financial savings and clinical impact of TEM-PCR

The CDC recommends that droplet precautions should be implemented for patients with suspected or confirmed influenza for seven days after illness onset or until 24 h after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a healthcare facility [2]. In addition, the CDC guidelines state that patients with complicated influenza receive at least five days of antiviral oseltamivir treatment [2]. At Huntsville Hospital, the H1N1 protocol included an average of 14 days of isolation, 10 days of oseltamivir treatment, and ±8 days of antibacterial medication [1 g vancomycin/12 h and 4.5 g Zosyn® (piperacillin and tazobactam)/8 h] depending on patient presentation. Patients' charts were reviewed for the date of admission, the date RIDT was performed, dates of oseltamivir doses, dates and frequency of antimicrobial therapy, isolation days, and the date TEM-PCR results were received. Using these dates, calculations in Supplementary Table I measured the clinical impact of TEM-PCR in number of days of isolation and medication use.

H1N1 isolation room costs per day from Zarogoulidis *et al.* were applied to this study, euros (€) were converted to US dollars ($), and 2010 costs were adjusted to 2014 to account for inflation [5]. Cost per day of isolation supplies from Hubben *et al.* were modified from 2007 to reflect inflated costs in 2014 [6]. Inflation calculations were done on the Consumer Price Index (CPI) calculator on the Bureau of Labor Statistics web site. Costs of oseltamivir and RIDTs were taken from pharmacy and billing data at Huntsville Hospital. TEM-PCR cost was taken from billing data at Diatherix.

Results

Of the 163 patients tested by both RIDT and TEM-PCR, 43 (26.4%) patients tested positive via TEM-PCR and negative via RIDT (Supplementary Table II). When evaluated with TEM-PCR as the gold standard, the sensitivity of the RIDT was 18.7%. The negative predictive value (NPV) was 71.3% whereas the positive predictive value (PPV) was 76.9%. There was substantial disagreement between RIDT and TEM-PCR results (Cohen's kappa of 0.201, $P < 0.0001$, McNemar's test with continuity correction).

Physicians isolated 13 (30.2%) of the 43 patients that initially received false-negative RIDT results, but delayed a total of 83 days of oseltamivir [mean: 6.4 days ± 5.3 (standard deviation) per patient] until TEM-PCR results confirmed the presence of H1N1 (Figure 1A). For five (11.6%) of the 43 patients that received empiric therapy the day of admission, a total of 14 isolation days (mean: 2.8 ± 0.8 days per patient) were withheld until confirmation of H1N1 by TEM-PCR (Figure 1B). Ten (23.3%) of the 43 patients had both oseltamivir and isolation deferred by 28 days (mean: 2.8 ± 1.9 days per patient) and 51 days (mean: 5.1 ± 5.4 days per patient), respectively (Figures 1A,B). A total of 111 days of oseltamivir were delayed in 23 patients (mean: 4.8 ± 4.5 days per patient) and 65 days of isolation were withheld in 15 patients (mean: 4.3 ± 4.5 days per patient) who had a false-negative RIDT (Figures 1A,B). Additionally, after TEM-PCR had verified that H1N1 was the only infection present, antibiotics were stopped in six patients, saving a total of 15 days (mean: 2.5 ± 1.6 days per patient) of antibiotic usage.

Of the 246 patients, 71 (28.9%) were treated as if they had H1N1 upon the date of admission, but were later found to be H1N1 negative via TEM-PCR. Forty-one (57.5%) of the 71 patients presented flu-like symptoms and were started on a 10 day treatment of oseltamivir, but isolation was delayed. After TEM-PCR tests were negative for H1N1, antivirals were stopped and 281 days (mean: 6.9 ± 1.7 days per patient) of oseltamivir therapy were saved (Figure 1C). TEM-PCR-negative patients experienced an average of 3.2 days of antiviral therapy instead of the suggested 10 days. Of the 71 patients, 11 (15.5%) patients were expected to be isolated for 14 days because of the possibility of H1N1 infection, but oseltamivir medication was withheld until secondary results were received. In all, 115 days of isolation (mean: 10.5 ± 2.5 days per patient) were saved as patients only averaged 3.6 days of excessive isolation instead of the scheduled 14 after TEM-PCR had determined that H1N1