The Effects of a Systemwide Diagnostic Stewardship Change on West Nile Virus Disease Ordering Practices

Andrew H. Karaba*1, Paul W. Blair*1,2, Kevin Martin3, Mustapha O. Saheed4, Karen C. Carroll5, and Michael J. Borowitz3

*These authors contributed equally to this work

1. Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

2. Austere environments Consortium for Enhanced Sepsis Outcomes (ACESCO), Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD

3. Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD

4. Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

5. Division of Medical Microbiology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD

Corresponding Author:

Michael J. Borowitz, mborowit@jhmi.edu

Weinberg 2237 Pathology

401 North Broadway

Baltimore, MD 21231

(410) 614-2889

© The Author(s) 2019. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Keywords: West Nile virus, Viral Encephalitis, Viral Diagnostics

Author Contributions:
AHK: designed study, analyzed data, prepared manuscript
PWB: designed study, analyzed data, prepared manuscript
KM: collected data, prepared manuscript
MOS: designed study, prepared manuscript
KCC: designed study, collected data, analyzed data, prepared manuscript
MJB: designed study, collected data, analyzed data, prepared manuscript

Abstract:
We report that removing the clinically insensitive West Nile virus CSF nucleic acid amplification test (NAAT) from the electronic health record (EHR) test menu decreased costs and may have improved diagnostic yield. Removing high-cost, low yield tests from the EHR can be an effective diagnostic stewardship intervention.

Introduction:
West Nile virus (WNV) is a flavivirus that exists in a transmission cycle between mosquitos and birds (1). It acts as a zoonotic infection when infected Culex spp. mosquitos transmit it to humans who are considered dead-end hosts (2). Since its
emergence in North America in 1999 it has remained endemic and caused thousands of cases each year in the United States (3,4).

While the precise incubation period for clinically apparent infections is unknown, in immunocompetent individuals it is thought to be between 2 and 14 days (1,5). About three-fourths of infections are likely clinically inapparent, while around 25% will develop WNV fever and <1% develop West Nile virus neuroinvasive disease (WNV-ND) (1). In contrast, as many as 1 in 50 patients older than 65 develop WNV-ND (6). Full recovery is common among patients with WNV fever, but WNV-ND is often complicated by severe neurologic sequelae. Patients often experience prolonged recovery of neurological function or even death (7,8).

Diagnosis of WNV-ND is based on appropriate laboratory testing in the right clinical scenario. The IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) is thought to be positive in more than 90% of patients within 8 days of symptom onset(9). The test is available through commercial laboratories. A positive MAC-ELISA in the cerebrospinal fluid (CSF) is highly suggestive of a WNV infection, but due to cross reactivity with other arboviruses, should be confirmed with a plaque-reduction neutralization testing (PRNT), or detection of WNV nucleic acid via nucleic acid amplification test (NAAT). Although NAAT is analytically highly sensitive (detection at 10-100 copies/mL), the short duration of viremia and often low amounts of virus in the CSF results in a low clinical sensitivity (4%-57%) (9,10). Additionally, NAAT is more expensive than the MAC-ELISA. Therefore, the CDC recommends testing for WNV using the MAC-ELISA rather than NAAT (11).
In an effort to increase the use of the MAC-ELISA and to decrease unnecessary PCR testing, CSF NAAT was removed from the test menu of the EHR of a five-hospital health system. Subsequently, we analyzed data from the EHR to determine the effectiveness of this intervention in reducing the use of the NAAT, decreasing costs, and detecting cases of probable WNV-ND. We hypothesized that removing the NAAT from the EHR ordering menu would decrease the amount of NAATs ordered and increase the use of the MAC-ELISA.

**Methods:**

In April 2018, the CSF WNV NAAT was removed from the test menu within the EHR of a health system comprising two academic hospitals in Baltimore, Maryland and three community hospitals (Maryland and Washington D.C.). NAAT ordering remained possible via a paper order. House officers were provided brief education about this change. We then reviewed WNV testing done on CSF samples obtained from patients at those hospitals from July 2016 through December 2018. The primary objectives were to compare the number of MAC-ELISA and NAAT WNV tests ordered before and after the change to the ordering protocol. The secondary objectives were to determine if this change led to any cost savings or changes in the detection rate of WNV-ND. The monthly, seasonal, and yearly number of positive test results, total test results, and total costs were determined from July, 2017 to April, 2018 compared to May, 2018 to January, 2019. A paired t-test was performed to evaluate for differences in total testing, total positive, and total costs during non-winter months before and after the intervention. Positive test results were clinically adjudicated independently by two infectious diseases physicians.
Results:

Both the WNV CSF MAC-ELISA and the NAATs were available to order at all hospitals in the health system during the study period. The cost incurred by the hospital for the NAAT was $150 per test during the study period and an average of $17 for the MAC-ELISA.

An average of 12.6 MAC-ELISA tests were performed per month (95% CI: 10.3, 14.9) prior to the intervention. This increased to an average of 41 MAC-ELISA tests/month (95% CI: 34.4, 47.7) in the post-intervention period which was statistically significant (p-value < 0.001). In contrast, there was an average of 46.2 NAATs/month (95% CI: 39.6, 52.9) before the intervention which decreased to 0 NAATs/month afterwards (p-value < 0.001) (Figure 1A). Additionally, the average number of WNV tests (MAC-ELISA + NAAT) performed decreased from 58.8 tests/month (95% CI: 51.0, 66.6) to 41.0 tests/month (95% CI: 34.4, 47.6) after the ordering intervention (p-value = 0.007). Comparing just the non-winter months, the average number of NAATs ordered per month decreased from 49.7 tests/month (95% CI: 41.3, 58.0) to 0 tests/month after the intervention. In contrast, the average number of MAC-ELISA tests ordered per month increased from 14.3 (95% CI: 12.0, 16.7) to 44.0 (95% CI: 39.1, 48.9) (Figure 1A).

Because of the difference in cost, the intervention resulted in a 93.5% decrease in WNV-ND test spending from an average of $7199.76 per month to $471.00 per month (p-value < 0.001) (Figure 1B). In addition, preceding the intervention, 0.23 % of all WNV CSF tests were positive (NAAT+MAC-ELISA) while 2.44% WNV CSF tests
were positive after the intervention (p-value = 0.03) (Figure 1A). No positive NAATs were reported during the study period. In contrast, there were 3 positive MAC-ELISA tests prior to the intervention and 9 positive results after the intervention (all during non-winter months). Of these, 8 were determined to be true positives and 1 considered not clinically consistent with WNV-ND.

Discussion:

A significant amount of health care dollars are wasted each year on inappropriate ordering of lab tests. Recently, diagnostic stewardship interventions have effectively used the EHR to reduce unnecessary testing for gastrointestinal infections and rheumatologic disorders (12,13). Here we demonstrate a simple solution to the problem of improper ordering of WNV NAAT by removing it as an option from the EHR test menu and providing brief education to house officers.

By engaging the appropriate departments (i.e. medicine, emergency medicine, neurology, and pathology) we were able to successfully make this change. Instrumental in making the change was communicating the CDC guidelines to stakeholders, and also demonstrating to them that we historically had a 0% positivity rate with the NAAT. While this was a positive change for clinical practice reasons, it also resulted in dramatically decreased costs.

Furthermore, the intervention was associated with an increase in the number of positive WNV CSF tests. This may be due to the increased sensitivity of the MAC-ELISA compared to the NAAT. However, the CDC reported 11 cases of WNV-ND in Maryland in 2018, but only 6 and 5 in 2016 and 2017, respectively (14). Therefore, the
increased detection could also be explained by the increased incidence during the year of the intervention. Interestingly, no positive NAATs were found during the study period, further supporting the poor utility of this as the primary test for WNV-ND.

A limitation of this study is that it was designed as a quality improvement study and we were not able to analyze relevant patient-level clinical data including how many patients also had serum testing for WNV or the time between symptom onset and testing in those that had negative testing. Therefore, we do not know if clinicians became more discriminating in their ordering after our brief meetings with house staff. While other flaviviruses may cross react with the WNV MAC-ELISA (1), the false positive rate was low in this study (0.11). However, serological testing may be negative in patients who present very early (<3 days) after onset of symptoms or who are immunosuppressed (15). It is unclear how many patients with negative testing would have fit these criteria.

This study also suggests that significant knowledge gaps exist regarding WNV disease. Prior to the ordering change, NAAT was performed 3.7 times more often than MAC-ELISA. NAAT may have been erroneously regarded as a more sensitive test extrapolating from other disease processes, or from confusion between analytical and clinical sensitivity. In addition, although WNV-ND is extremely rare during winter (16), a significant number of NAATs were ordered in winter, suggesting that providers do not appropriately judge prior probabilities in their decision to order NAAT.

It is important to note that NAAT remained available to order, but the process required filling out paperwork. During the follow-up study period, there were no paper NAAT orders placed potentially due to the perceived high time cost. The data presented
here cannot directly address either the indications for the tests or the motivations for the providers, but systematic “nudges” to improve diagnostic stewardship should be further researched.

In conclusion, elimination of electronic ordering is an effective way of decreasing inappropriate WNV NAAT ordering, decreasing associated costs, and may lead to improved diagnosis of WNV-ND. In reducing low-yield testing, evidence-based selection of EHR test menu options is an effective strategy to improve diagnostic accuracy of relatively uncommon or rare diseases.

Acknowledgments:

Financial Support: This work was supported by the National Institutes of Health T32 AI007291-27 to AHK and PBW. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Figure 1. West Nile virus CSF testing and costs from July, 2016 to January, 2019. A. Total NAATs (blue bars, left axis), total IgM (MAC-ELISA) tests (grey bars, left axis), positive NAATs (orange bars, right axis), and positive IgM tests (purple bars, right axis) for each indicated month (x-axis) are shown. Dissemination of information to house officers began March 2018. A red arrow indicates the time of removal of WNV NAAT from the order test menu (May 2018).
B. NAAT costs (orange bars) and IgM test costs (blue bars) in U.S. dollars for each month are shown. A red arrow indicates the time of removal of WNV NAAT from the order test menu (intervention).

References:

1. Petersen LR, Brault AC, Nasci RS. West Nile Virus: Review of the Literature. JAMA. 2013; 310(3):308–19.

2. Kramer LD, Li J, Shi P-Y. West Nile virus. The Lancet Neurology. 2007; 6(2):171–181.

3. Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001; 344(24):1807–1814.

4. Burakoff A, Lehman J, Fischer M, Staples JE, Lindsey NP. West Nile Virus and Other Nationally Notifiable Arboviral Diseases — United States, 2016. Morbidity and Mortality Weekly Report. Centers for Disease Control and Prevention; 2018; 67(1):13–17.

5. Pealer LN, Marfin AA, Petersen LR, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med. 2003; 349(13):1236–1245.

6. Carson PJ, Borchartd SM, Custer B, et al. Neuroinvasive Disease and West Nile Virus Infection, North Dakota, USA, 1999–2008. Emerg Infect Dis. 2012; 18(4):684–686.

7. Emig M, Apple DJ. Severe West Nile virus disease in healthy adults. Clinical Infectious Diseases. 2004; 38(2):289–292.

8. Klee AL, Maidin B, Edwin B, et al. Long-term prognosis for clinical West Nile virus infection. Emerg Infect Dis. 2004; 10(8):1405–1411.

9. Barzon L, Pacenti M, Ulbert S, Palù G. Latest developments and challenges in the diagnosis of human West Nile virus infection. Expert Rev Anti Infect Ther. Informa Healthcare; 2015; 13(3):327–342.

10. Murray KO, Walker C, Gould E. The virology, epidemiology, and clinical impact of West Nile virus: a decade of advancements in research since its introduction into the Western Hemisphere. Epidemiol Infect. 2011; 139(6):807–817.

11. https://www.cdc.gov/westnile/healthcareproviders/healthCareProviders-Diagnostic.html Aug 6, 2019
12. Marcelin JR, Brewer C, Beachy M, et al. Hardwiring diagnostic stewardship using electronic ordering restrictions for gastrointestinal pathogen testing. Infect Control Hosp Epidemiol. 2019; 40(6):668–673.

13. Barry C, Kaufman S, Feinstein D, et al. Optimization of the Order Menu in the Electronic Health Record Facilitates Test Patterns Consistent With Recommendations in the Choosing Wisely Initiative. Am J Clin Pathol. 2019.

14. West Nile virus: statistics & maps. https://www.cdc.gov/westnile/statsmaps/index.html. Fort Collins.

15. Hiatt B, DesJardin L, Carter T, Gingrich R, Thompson C, de Magalhaes-Silverman M. A fatal case of West Nile virus infection in a bone marrow transplant recipient. Clinical Infectious Diseases. 2003; 37(9):e129–31.

16. Groves JA, Shafi H, Nomura JH, et al. A probable case of West Nile virus transfusion transmission. Transfusion. John Wiley & Sons, Ltd (10.1111); 2017; 57(3pt2):850–856.
Figure 1.