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Utility of Rapid Influenza Molecular Testing in an Outpatient Hemodialysis Unit: A Prospective Cohort Study

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Abstract

Background: Early initiation of antiviral therapy for individuals at risk for severe influenza infection is important for improving patient outcomes. Current guidelines recommend empiric antiviral therapy for patients with end-stage kidney disease presenting with suspected influenza infection. Rapid molecular influenza assays may reduce diagnostic uncertainty and improve patient outcomes by providing faster diagnostics compared to traditional batched polymerase chain reaction (PCR) testing.

Objective: To determine the utility of implementing a rapid influenza PCR assay compared to the standard of care in a hemodialysis unit.

Design: This is a prospective cohort study.

Setting: A hospital-based dialysis unit in a tertiary care hospital.

Patients: Adult patients with end-stage kidney disease on intermittent hemodialysis.

Measurements: Patient characteristics, influenza PCR swab results, antibiotic prescriptions, antiviral prescriptions, emergency room visits and hospitalizations.

Methods: From November 1, 2017 to March 31, 2018, we assigned samples collected from a single center, hemodialysis unit to be processed using a rapid influenza PCR (cobas® Influenza A/B & respiratory syncytial virus assay) or the standard of care (in-house developed multiplex PCR). Samples were assigned to the rapid PCR if the patient received dialysis treatment in the morning dialysis shift, while the remainder were processed as per standard of care. Study outcomes included the time from collection to result of nasopharyngeal swab, prescription of influenza antiviral therapy, time to receiving prescription, and the need for emergency department visit or hospitalization within 2 weeks of presentation.

Results: During the study period, 44 patients were assessed (14 with the rapid PCR and 30 with the standard of care assay). Compared to conventional testing, the time to result was shorter using rapid PCR compared to conventional testing (2.3 vs 22.6 hours, $P < .0001$). Individuals who were tested using the rapid PCR had a tendency to shorter time to receiving antiviral prescriptions (0.7 days vs 2.1 days, $P = .11$), and fewer emergency department visits (7.1% vs 30%, $P = .13$) but no difference in hospitalizations (14.3% vs 30%, $P = .46$) within 2 weeks of testing.

Limitations: This is a single center non-randomized study with a relatively small sample size. Patients who were tested using the standard of care assay experienced a delay in the prescription of antiviral therapy which deviates from recommended clinical practice.

Conclusions: Rapid influenza molecular testing in the hemodialysis unit was associated with a shorter time to a reportable result and with a tendency to reduced time to prescription of antiviral therapy. Rapid molecular testing should be compared with standard of care (empiric therapy) in terms of economic costs, adverse events, and influenza-related outcomes.

Abrégé

Contexte: L'initiation précoce d'un traitement antiviral est essentielle pour améliorer les résultats de santé des personnes exposées à un grand risque d'infection grippale. Chez les patients atteints d'insuffisance rénale terminale (IRT) suspectés d'une infection grippale, les recommandations actuelles préconisent une approche empirique de traitement antiviral. Les

tests moléculaires de dépistage rapide du virus influenza peuvent réduire l'incertitude diagnostique et améliorer les résultats pour les patients en posant un diagnostic plus rapidement que les tests PCR en lots traditionnellement utilisés.
Objectif: Mesurer l'intérêt de mettre en place un test PCR de dépistage rapide de la grippe comparativement à la norme de soins d'une unité d'hémodialyse.
Type d'étude: Étude de cohorte prospective.
Cadre: Une unité de dialyze hospitalière de soins tertiaires.
Sujets: Des adultes atteints d'IRT et traités par hémodialyse intermittente.
Mesures: Les caractéristiques des patients, les résultats de dépistage du virus influenza, les prescriptions d'antibiotiques et d'antiviraux, les visites à l'urgence et les hospitalisations.
Méthodologie: Entre le 1er novembre 2017 et le 31 mars 2018, les échantillons prélevés à l'unité d'hémodialyse du center ont été répartis pour être analysés soit par la méthode PCR de dépistage rapide (*cobas®Essai Influenza A/B & VRS*), soit par la méthode traditionnellement utilisée (PCR multiplex mises au point à l'interne). Les prélèvements des patients dialysés pendant le quart de travail du matin ont été assignés à la méthode rapide, les autres ont été testés par la méthode traditionnelle. Les résultats incluaient le délai entre le prélèvement et le résultat de l'écouvillonnage naso-pharyngé, la prescription d'un traitement antiviral, le temps requis pour obtenir la prescription et la nécessité de se rendre à l'urgence ou d'être hospitalisé dans les deux semaines suivant la présentation des symptômes.
Résultats: Au cours de l'étude, 44 patients ont été diagnostiqués avec la méthode rapide par PCR (n=14) ou la méthode traditionnelle (n=30). Comparativement à la méthode traditionnelle, la méthode rapide par PCR a permis de réduire le temps d'obtention du résultat (2,3 h contre 22,6 h pour la méthode traditionnelle; $P < .0001$). Les patients diagnostiqués avec la méthode rapide par PCR tendaient à obtenir une ordonnance d'antiviraux plus rapidement (0,7 jour contre 2,1 pour la méthode traditionnelle; $P = .11$) et à avoir visité l'urgence moins souvent (7,1 % contre 30 % pour la méthode traditionnelle, $P = .13$), mais ne présentaient aucune différence significative dans le nombre d'hospitalisations (14,3 % contre 30 % pour la méthode traditionnelle; $P = .46$) dans les deux semaines de suivi.
Limites: Il s'agit d'une étude non répartie aléatoirement, qui s'est tenue dans un seul center et sur un échantillon relativement restreint. Les patients diagnostiqués avec la méthode traditionnelle ont subi un retard dans la prescription du traitement antiviral, ce qui s'écarte de la pratique clinique recommandée.
Conclusion: Chez les patients d'une unité d'hémodialyse, le dépistage moléculaire rapide du virus influenza a été associé à un diagnostic plus rapide et à une tendance à une réduction du délai de prescription du traitement antiviral. Il serait pertinent de comparer le dépistage moléculaire rapide avec la norme standard de soin (traitement empirique) en ce qui concerne les coûts, les événements indésirables et les issues de santé liées à la grippe.

Keywords
influenza, hemodialysis, rapid influenza PCR, nasopharyngeal swab

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What was known before

Rapid influenza assays have been associated with improved patient outcomes compared to traditional polymerase chain reaction (PCR) testing in certain populations.

What this adds

This is the first study, in our knowledge, to evaluate the impact of rapid influenza molecular assays on patient outcomes in the hemodialysis unit setting.

Introduction

Early diagnosis of influenza in patients presenting with influenza-like illness (ILI, defined as an acute respiratory tract infection with a fever ≥38°C and cough)[1] can contribute to a reduction in risk of hospitalizations, prevention of transmission/outbreaks, and receipt of inappropriate antibiotic therapy.[2,3] In Canada, it is estimated that influenza causes approximately 12,200 hospital admissions and 3500 deaths annually.[4] In the United States alone, the economic burden of seasonal influenza has been estimated to be $11.2

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billion annually due to increased health care resource utilization and days of work productivity lost.[5] Early initiation of antiviral therapy for patients with influenza infection is associated with a shorter duration of symptoms, and early treatment may reduce the overall burden of health care–related complications in selected patient populations, although evidence in dialysis-dependent patients is limited.[6] Current guidelines recommend prompt initiation of therapy with antivirals within 48 hours of symptom onset for patients at a higher risk for complications without waiting for confirmation of influenza infection through laboratory testing.[7,8] However, there may be diagnostic uncertainty in patients presenting with ILI. This uncertainty can lead to unnecessary treatment with antibiotics, investigations, and hospitalizations.

Influenza testing reduces clinical diagnostic uncertainty and allows for targeted antiviral therapy, but the utility of this test can be limited if the result is not immediately available. Rapid influenza antigen tests (non-molecular) offer results within 15 to 30 minutes, but are limited by poor sensitivity. Standard PCR assays have improved sensitivity and are now standard of care in the acute care setting[9]; however, these assays are often batched daily at specialized laboratories, increasing turnaround time.[10] Newer commercial random access rapid molecular tests have been introduced, which maintain the sensitivity of PCR but reduce turnaround times (20-120 minutes),[11] and may help address the need for a rapid accurate diagnostic test.

Rapid PCR influenza tests may result in reduced antibiotic prescriptions, increased antiviral prescriptions, and reduced length of stay in emergency department (ED).[12-16] Much of the literature regarding rapid influenza testing has been based on rapid antigen tests or batched PCR testing, with comparatively fewer studies reporting the utilization of newer rapid molecular tests. In addition, the available literature focuses on pediatric populations, developing countries, or patient populations presenting to ED. The benefit of rapid PCR influenza testing in high-risk outpatient departments such as hemodialysis units is currently unknown.

Individuals who are dependent on hemodialysis for treatment of end-stage kidney disease (ESKD) represent a high-risk outpatient population for complications of influenza infection.[7,17,18] In addition, there is a significant risk of spreading communicable diseases from one patient to another within the hemodialysis unit, due to the requirement for frequent (3-4 times per week) hemodialysis treatments, the close proximity of patients, and the lack of private rooms in most hemodialysis units.[19]

In this study, we prospectively evaluated the use of a new rapid, commercial PCR influenza test compared to the standard influenza testing for patients being treated in a hospital-based hemodialysis unit. To our knowledge, this is the first prospective evaluation of the utility of rapid PCR influenza testing in a hemodialysis unit.

Methods

Study Population

We conducted a single-center, prospective study in an tertiary-care hospital outpatient hemodialysis unit in Vancouver, Canada, between November 1, 2017 and March 31, 2018. Individuals requiring hemodialysis treatment in this unit are routinely assigned to either a morning, afternoon, or evening treatment time recurring 3 times per week (ie, Monday, Wednesday, and Friday, or Tuesday, Thursday, and Saturday/Sunday). This hemodialysis unit is typically responsible for the care of approximately 260 hemodialysis-dependent adult patients with ESKD at any given time.

Study Intervention

During the period of study recruitment, nasopharyngeal flocked swabs from patients in the hemodialysis unit were either processed using the rapid PCR (cobas® Influenza A/B & RSV, Roche Molecular Diagnostics, Pleasanton, CA, USA on the Liat® system) or the current standard of care, in-house developed multiplex PCR assay, which includes influenza A/B, respiratory syncytial virus (RSV), human metapneumovirus, parainfluenza 1/2/3, and adenovirus.[20] Swabs collected from individuals who received their hemodialysis treatment in the morning were processed using the rapid influenza PCR, while swabs taken from patients receiving their hemodialysis treatment in the afternoon or evening sessions were batched and processed using the standard assay. The results from the rapid PCR influenza assay could be available as soon as 30 minutes after being received by the virology laboratory, and therefore were available during the hemodialysis session during which the swab was collected. In contrast, the standard of care assay results would become available the following day, as they were batched and tested once daily. The laboratory telephoned all positive results to the hemodialysis unit. Results were also available in patients' electronic medical records. Positive results for influenza A or B (or other respiratory viruses) were then directly communicated to the healthcare provider responsible for patient care as per routine practice. All patients with suspected or confirmed influenza were placed on droplet/contact precautions (in order to minimize the risk of transmission of the influenza virus in the unit).

Aside from the assignment of the assay platform, there was no other direct intervention from the study on the evaluation and treatment of individuals with suspected influenza. The evaluation and treatment of individuals with suspected influenza was entirely at the discretion of the healthcare provider (either a physician or nurse practitioner). This included any decision to initiate antiviral therapy or antibiotic therapy, or pursue other diagnostic testing. For individuals tested using the rapid influenza assay, results were available during the clinical encounter to inform decision making, while for

Table 1. Baseline Demographics and Presenting Symptoms of Patients Included in This Cohort of 44 Hemodialysis Patients Tested for Influenza Between November 1, 2017 and March 31, 2018, Stratified by Testing Platform.

Variable	Rapid PCR ($n = 14$)	Standard of care PCR ($n = 30$)	*P*-value
Age—years (mean [SD])	71.0 (10.8)	67.6 (15.1)	.61
Sex (%)			1.00
Female	5 (35.7)	12 (40.0)	
Male	9 (64.3)	18 (60.0)	
Duration of dialysis therapy—years (mean [SD])	3.64 (3.12)	3.32 (3.61)	.84
Cause of end-stage kidney disease (%)			.49
Hypertension	2 (14.3)	3 (10.0)	
Diabetes	3 (21.4)	13 (43.3)	
Glomerulonephritis	5 (35.7)	5 (16.7)	
Other	4 (28.6)	4 (13.3)	
Influenza vaccination in past year (%)			.54
Yes	13 (92.9)	29 (96.7)	
No	1 (7.1)	1 (3.3)	
Symptoms present at presentation (%)			
Cough	13 (92.9)	20 (66.7)	.08
Fever	1 (7.1)	7 (23.3)	.40
Shortness of breath	3 (21.4)	8 (26.7)	1.0
Malaise	2 (14.3)	5 (16.7)	1.0
Other symptoms[a]	1 (7.1)	5 (16.7)	.65

Note. PCR = polymerase chain reaction; SD = standard deviation.
[a]Other symptoms reported included nasal discharge, rigors, wheeze, and sore throat.

individuals testing on the standard of care assay, results would not become available until the following day. All physicians and nurses practicing in this hemodialysis unit were provided with education on the indications and guidelines for influenza testing prior to study implementation.

Outcomes

Patient demographics were collected for all individuals who had a nasopharyngeal swab submitted for respiratory virus testing. All symptoms of influenza were documented at each hemodialysis treatment by the nursing staff. Prescriptions of antibacterial or antiviral agents were documented prospectively. The study outcomes included (1) time from collection to result of nasopharyngeal swab (turnaround time), (2) prescription of antibacterial agents, (3) prescription of influenza antiviral therapy, (4) time to receiving prescription of influenza antiviral therapy, and (5) the need for ED visit or hospitalizations within 2 weeks of presentation. These outcomes were assessed at each hemodialysis session.

Statistical Analysis

Baseline patient demographics and study outcomes of all individuals who underwent testing with a nasopharyngeal swab were described using means with standard deviations or proportions as appropriate, stratified by testing platform. Testing for statistically significant differences between the rapid influenza PCR and standard of care groups was performed using the Wilcoxon rank-sum test or the Fisher exact test where appropriate. A *P*-value less than or equal to .05 was used to determine statistical significance. All statistical analyses were conducted using R software.[21] This study received ethics approval from the University of British Columbia—Providence Health Care Research Ethics Board (H17-01779-A003).

Results

Cohort Description

During the study interval, a total of 45 nasopharyngeal swabs for suspected influenza infection were collected. One individual was tested twice, approximately 2 months apart, and 1 sample was never processed due to incorrect sample collection. Fourteen patient samples were processed using the rapid PCR influenza assay, while 30 were processed using the standard of care assay. The difference in the use of rapid versus the standard of care assay during the study were expected, as the rapid assay was only used for patients assigned to the morning dialysis shift, while the standard of care assay was applied to afternoon and evening dialysis shifts. The baseline demographics and presenting symptoms of the patients who underwent testing, stratified by the testing platform, are presented in Table 1. The group tested on the rapid influenza assay was slightly older and had a longer

Table 2. Outcomes of All Individuals (N = 44) Tested for Influenza Between November 1, 2017 and March 31, 2018, Stratified by Testing Platform.

Variable	Rapid PCR (n = 14)	Standard of care PCR (n = 30)	P-value
Mean time to result in hours (SD)	2.32 (1.31)	22.62 (5.45)	<.0001
Diagnosis of influenza (%)			1.0
Yes	3 (21.4)	8 (26.7)	
No	11 (78.6)	22 (73.3)	
Need for ER visit within 2 weeks (%)			.46
Yes	2 (14.3)	9 (30.0)	
No	12 (85.7)	21 (70.0)	
Need for hospital visit within 2 weeks (%)			.13
Yes	1 (7.1)	9 (30.0)	
No	13 (92.9)	21 (70.0)	

Note. PCR = polymerase chain reaction; ER = emergency room; SD = standard deviation.

mean duration of dialysis therapy. There were more patients with diabetes as the cause of ESKD in the group tested on the standard of care assay. None of the differences between these groups were statistically significant. Only 1 individual in each group did not have a documented influenza vaccination within the previous year. The most common symptom at presentation was a cough in both groups. This was followed by shortness of breath, fever, and malaise. Six patients experienced other symptoms which included nasal discharge and vomiting. There was no statistically significant difference in the symptoms at presentation between the 2 groups.

Of the 44 nasopharyngeal swabs processed during the study period (1 was rejected due to improper specimen collection), 3 (21.4%) were positive for influenza in the rapid PCR group, and 8 (26.7%) were positive in the standard of care group (Table 2). The difference in percentage of positive results was not statistically significant between the 2 groups (P = 1.0). Seven of these swabs identified as influenza A and 4 identified influenza B. Three samples were positive for RSV, and no viruses were detected in the remainder of the samples. The mean time from collection to receipt of a result in the rapid PCR group was 2.3 hours which was over 20 hours shorter than the standard of care group (Table 2). This difference was statistically significant (P-value < .0001). Only 2 patients in the rapid PCR group (14.3%) required an ED visit in the 2 weeks following the nasopharyngeal swab compared with 9 patients (30.0%) in the standard of care group. One patient (7.1%) in the rapid PCR group required hospitalization within 2 weeks following testing compared with 9 patients (30.0%) in the standard of care group. These differences were not statistically significant (P-values of .46 and .13, respectively).

All the patients with a positive PCR result for influenza in both groups subsequently received an oseltamivir prescription. The mean time to prescribing oseltamivir was 0.7 days in the rapid PCR group and 2.1 days in the standard of care group. This difference was not statistically significant (P-value = .11). Only 1 patient with a negative swab received an oseltamivir prescription; this patient was in the standard of care group.

Three individuals (1 in the rapid PCR group and 2 in the standard of care group) who had a positive PCR for influenza also received treatment with antibiotics within 2 weeks of testing. One of these patients in the standard of care group was diagnosed with multi-lobar pneumonia which progressed despite antiviral therapy, while the patient in the rapid PCR group had a positive sputum culture for *Haemophilus influenzae*. The third patient developed appendicitis requiring antibiotic therapy. Seven individuals who had a negative PCR for influenza received treatment with antibiotics within 2 weeks of testing. All of these patients also subsequently had documented bacterial infections with either positive blood or urine cultures, or radiographic and clinical evidence of pneumonia except for 1 individual in the rapid PCR group.

Discussion

Use of the rapid PCR influenza assay resulted in a substantially shorter time to result than the standard of care assay. Both rapid and standard of care testing were performed in the virology laboratory, as opposed to point of care. Despite specimens being transported to the laboratory, short turnaround times (2.3 hours) were still achieved for rapid testing, enabling the potential utilization of the rapid assay for other clinical needs within our healthcare facility.[3] A key aspect of our study was the delivery of quick turnaround times and the timely availability of laboratory results, with results being made available to healthcare providers before the patients' hemodialysis run was completed (and the patient subsequently discharged home). In this study, we did not find that rapid PCR testing resulted in a statistically significant difference in subsequent emergency room

visits or hospitalizations, potentially due to the smaller sample size. However, there is potential that rapid PCR testing in this population may have substantial impact on both patient outcomes and health care resource utilization in a larger cohort. Although not assessed in our study, there is also supplemental value in rapid influenza PCR testing as it may minimize the duration of infection control precautions in cases where testing is eventually negative, thus enhancing work-flow and decreasing costs.

Healthcare practitioners in this particular hemodialysis unit relied heavily on the influenza PCR results to establish treatment plans. This was clearly demonstrated given that only 1 patient who tested negative for influenza received a prescription for oseltamivir, while all patients who had a positive PCR test received a prescription for oseltamivir. This pattern of practice is not consistent with current guidelines which suggest that all dialysis-dependent patients receive empiric antiviral therapy at the time of presentation with ILI. This practice pattern may limit the generalizability of the results of this study. It is possible that this practice pattern is unique to this dialysis unit; however, data on the compliance of hemodialysis units in Canada with guideline recommendations are not currently available. It is possible that the inconvenience of administration of antivirals, which are not routinely supplied in the dialysis unit and that the antivirals are not covered under the provincial renal formulary may play a role in this divergence from recommended practice. The availability of a rapid diagnostic test in this setting shortened the time to prescription of oseltamivir by almost 1.5 days. This earlier introduction of antiviral therapies might substantially improve the efficacy of antiviral therapy in reducing symptoms and severity of influenza (including complications), particularly in an immunocompromised population, such as in individuals with ESKD.

In addition to the deviation from clinical practice recommended by guidelines, there are 2 other main limitations to this study. First, this study is not a randomized, controlled trial; rather, patients were assigned based on a pre-existing division of patients by dialysis treatment time. The decision to divide patients in this manner was based on pragmatic considerations, as resources were not available to conduct a randomized controlled trial. Given the non-random study design, there is potential for confounding between the 2 groups. Our dialysis unit preferentially schedules the more medically complex patients to be treated on the morning (rapid PCR) dialysis shift, which if anything, would bias negative outcomes to this group. The second key limitation is the sample size of the study. During the study design, we estimated that approximately 25% of all the individuals in the dialysis unit would undergo testing (~65 tests) and that up to 10% of the cohort would test positive for influenza given previous trends in influenza infection. Unexpectedly, there were only 44 tests collected and 11 individuals who developed influenza in the whole cohort over the study period. This unexpectedly low incidence of influenza and respiratory symptoms resulted in an inadequate sample size.

The sensitivity and specificity of the cobas® rapid PCR assay for the diagnosis of influenza A and B reported in the literature is excellent at 100 and 99.3% to 100%, respectively.[11] As a targeted influenza A/B and RSV assay, it is possible that with the rapid PCR influenza assay may lead to misdiagnosis of other viral illnesses which are not tested for on this platform, such as adenovirus, rhinovirus, human metapneumovirus, and parainfluenza viral infections. Should healthcare providers adopt the rapid PCR platform, understanding the limitation of the testing platform would be important to avoid potential misdiagnoses. It is also important to note that the results of this study may not apply to a community dialysis unit, where influenza testing must be sent to an offsite laboratory for processing. In these situations, there may be delays in the time to result regardless of the testing platform.

As a pilot evaluation of the use of rapid PCR testing in hemodialysis patients, cost-effectiveness was not specifically addressed, but such studies are needed to inform healthcare facilities attempting to adopt new technology. Due to limitations in generalizability, institutions considering implementing a rapid PCR assay should conduct their own cost-effectiveness evaluation, owing to the multitude of unique variables depending on the clinical setting. From the laboratory, cost differential is dependent on factors such as existing workflow (and technologist time to perform the test), type of assay utilized, and volume of testing performed. Similarly, variations in clinical practice exist as demonstrated in this setting where patients who were tested with the standard of care assay had a delay in the prescription of oseltamivir. However, routine implementation of rapid PCR testing in the hemodialysis unit may be cost-saving compared to the standard of care assays if rapid testing obviated the need for oseltamivir prescriptions, unnecessary antibiotic prescriptions, and fewer unnecessary other diagnostic tests and hospitalizations. Previous publications suggest that rapid PCR testing compared to standard of care may be cost-effective in the context of hospitalized patients or patients presenting with ILI to the emergency room depending on the prevalence of influenza.[22-25] Although patient outcomes in this study were not significantly different by rapid PCR testing, given the overall potential benefits of rapid reporting of influenza results, our institution has implemented rapid molecular testing for patients with suspected ILI as first line testing. Patients with a transplant, history of HIV with a CD4 count less than 200 cells/mm^3, or those in a critical care setting would still have a rapid molecular test to enable quick reporting, followed by the multiplex assay to investigate for other respiratory viruses.[26]

Conclusion

Overall, the use of rapid PCR influenza testing resulted in faster reporting of results for influenza compared with the standard of care assay. This may contribute to optimization of antiviral prescriptions and potentially lower ED visits and

hospitalizations, although these were not statistically significant in this study. Further study in a larger cohort is required to compare rapid molecular testing with standard of care (empiric therapy) in terms of economic costs, adverse events, and influenza-related outcomes.

Ethics Approval and Consent to Participate

Ethics approval for this research was received from the UBC - Providence Health Care Research Ethics Board (H17-01779). The requirement of participant consent was waived given the minimal risk to study participants.

Consent for Publication

All authors consent to the publication of this manuscript.

Availability of Data and Materials

Data queries can be addressed to Dr. Matthew Kadatz via email at matthew.kadatz@vch.ca.

Authors' Note

The results of this prospective study were presented at the AMMI Canada—CACMID Annual Conference as a poster abstract on April 1, 2019 in Ottawa, Ontario, Canada.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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