Interferon Alfacon-1 Plus Corticosteroids in Severe Acute Respiratory Syndrome
A Preliminary Study

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Context
Severe acute respiratory syndrome (SARS) is a new clinical entity for which no effective therapeutic strategy has been developed.

Objective
To provide preliminary results on the potential therapeutic benefit and tolerability of interferon alfacon-1 plus corticosteroids for SARS.

Design, Setting, and Patients
Open-label study of 22 patients diagnosed as having probable SARS at North York General Hospital, Toronto, Ontario, between April 11 and May 30, 2003.

Interventions
Thirteen patients were treated with corticosteroids alone and 9 patients were treated with corticosteroids plus subcutaneous interferon alfacon-1.

Main Outcome Measures
Clinical parameters, including oxygen saturation and requirement, laboratory measures, and serial chest radiography results.

Results
Resolution of fever and lymphopenia were similar between the 2 treatment groups. Of the 13 patients treated with corticosteroids alone, 5 (38.5%) were transferred to the intensive care unit, 3 (23.1%) required intubation and mechanical ventilation, and 1 (7.7%) died. Of the 9 patients in the interferon alfacon-1 treatment group, 3 (33.3%) were transferred to the intensive care unit, 1 (11.1%) required intubation and mechanical ventilation, and none died. The interferon alfacon-1 treatment group had a shorter time to 50% resolution of lung radiographic abnormalities (median time, 4 days vs 9 days; \( P = .001 \)), had better oxygen saturation (\( P = .02 \)), resolved their need for supplemental oxygen more rapidly (median, 10 days vs 16 days; \( P = .02 \)), had less of an increase in creatine kinase levels (\( P = .03 \)), and showed a trend toward more rapid resolution of lactate dehydrogenase levels compared with the group receiving corticosteroids alone.

Conclusions
In this preliminary, uncontrolled study of patients with SARS, use of interferon alfacon-1 plus corticosteroids was associated with reduced disease-associated impaired oxygen saturation, more rapid resolution of radiographic lung abnormalities, and lower levels of creatine kinase. These findings suggest that further investigation may be warranted to determine the role of interferon alfacon-1 as a therapeutic agent for the treatment of SARS.

See also pp 3215, 3229, and 3251.
use of ribavirin has been associated with significant toxic effects. Hyperimmunoglobulin, protease inhibitors, fusion inhibitors, and interferons represent other therapeutic options for treating SARS patients. Among these possibilities, interferon alfa is a potential candidate agent and has been recognized to play critical roles in host resistance to viral infection. Interferons inhibit viral infection by inducing both innate and adaptive immune responses (eg, by altering the intracellular environment to restrict viral replication, and inducing signaling events that activate immune cell populations and thereby elicit an antiviral immune response).

Interferon alfas have been shown to be of value in the treatment of hepatitis B and C and to induce inhibition of respiratory coronavirus infections, albeit unrelated to the Urbani strain of SARS-CoV. In in vitro experiments, interferons were effective in cell culture systems and comparative clinical trials to inhibit viral replication more potently than other type 1 interferons.

This preliminary pilot study was initiated to evaluate the potential clinical benefit and safety of interferon alfacon-1 in SARS treatment.

METHODS
Patient Selection
The study population involved 22 patients who were admitted to North York General Hospital (NYGH), Toronto, Ontario, between April 11 and May 30, 2003, and met the Centers for Disease Control and Prevention and World Health Organization criteria for probable SARS. Inclusion criteria for interferon alfacon-1 therapy were: (1) symptom onset within 10 days of the Health Canada approval date (May 29, 2003) for use of interferon alfacon-1 in SARS patients; (2) progressive radiological deterioration over the preceding 48 hours, with greater than 20% involvement of lung fields; (3) progressive deterioration of clinical respiratory status over the preceding 48 hours (decreasing oxygen saturation, increasing respiratory rate, or worsening dyspnea); and (4) patient informed consent for use of interferon alfacon-1. Exclusion criteria included (1) symptom onset more than 10 days before the Health Canada approval date; (2) mechanical assisted ventilation in the intensive care unit (ICU); and (3) contraindication to use of interferon alfacon-1. Nine patients met the inclusion criteria for interferon alfacon-1 treatment.

Patients with probable SARS who were admitted to NYGH during the same period and were administered corticosteroids but not ribavirin served as a comparison group. After May 29, interferon alfacon-1 was offered to all patients who met inclusion criteria. Eleven patients who were admitted prior to May 30 and 2 who declined interferon alfacon-1 treatment comprise the comparison group. All patients admitted prior to April 11, 2003, were excluded because they were included in a previously published study and received ribavirin.

Treatment Protocols
Oral prednisone, 50 mg twice per day, or intravenous methylprednisolone, 40 mg every 12 hours, was administered to all patients who had abnormal chest radiographs. After May 26, 2003, patients exhibiting progressive disease, characterized by worsening chest radiographs, decreasing oxygen saturation, and worsening dyspnea, received pulsed high-dose intravenous methylprednisolone, 500 mg once per day, for 3 days, followed by a taper and a step down to oral prednisone to complete a 20-day course similar to the previously described protocol. Patients who required at least 6 L/min of oxygen via nasal prongs to maintain oxygen saturation of at least 92% were transferred to the ICU.

Following Health Canada approval for interferon alfacon-1 use in SARS treatment (May 29, 2003), interferon alfacon-1 was offered through a special access program to all patients who met inclusion criteria for interferon alfacon-1 treatment. Because this study represented the first use of interferon for SARS treatment, the Health Canada provisions for its use in these patients included consultation with an immunologist and submission of a report of adverse events. Institutional research ethics boards for NYGH and the University Health Network reviewed and approved the study protocol and written informed consent was obtained from all participants who received interferon alfacon-1.

Patients were administered subcutaneous interferon alfacon-1 for a total of 10 days, beginning with 9 µg/d for a minimum of 2 days and increased to 15 µg/d if no clinical response was observed. Of the 9 patients treated with interferon alfacon-1, 7 received only the 9-µg dose and 2 received the 15-µg doses. Because of concerns about possible viral and disease rebound if interferon alfacon-1 treatment was stopped before cessation of corticosteroids, a more rapid steroid taper was introduced and interferon alfacon-1 treatment was continued for 1 day after corticosteroid termination. Because of the variable stages of steroid tapering, the interferon alfacon-1 treatment courses ranged from 8 to 13 days. Patients were not discharged to home while still receiving interferon alfacon-1. Patients in the comparison group received corticosteroids but not ribavirin while at NYGH. These patients were chosen prior to data analysis. In both groups, supplemental oxygen therapy was withdrawn when oxygen saturation increased to at least 99% with 1 L/min of oxygen via nasal prongs and at the discretion of treating physicians.

Laboratory Studies and Chest Radiographs
Laboratory investigations included serum hematological and biochemical assays. Acute and convalescent serum
samples were tested for SARS-CoV–associated IgG, using both an enzyme-linked immunosorbent assay and an indirect immunofluorescent assay targeted to the SARS-CoV propagated in Vero E6 cells (National Reference Laboratory, Winnipeg, Manitoba). Serial chest radiographs were obtained from a total of 31 patients at NYGH, including the 22 study patients and 9 additional radiological controls. Radiological controls were randomly chosen from a list of patients investigated for but found not to have SARS and were included to ensure blinding to the disease and the treatment (results of these radiological controls are not included in the data analysis).

Each radiograph was obtained in the frontal projection and was retrospectively reviewed independently by 3 radiologists who were blinded to the identity, diagnosis, and treatment protocol of each patient. For each radiograph, description and an approximate size estimation of the abnormalities, based on percentage of lung involvement, were recorded. For quantitative assessment of radiographic disease progression, the mean percentage of lung involvement reported by the 3 readers was calculated for each radiograph. The radiographic end point used for the analysis was decided prior to any data analysis and was defined as the time from maximum to 50% improved chest radiographic abnormalities. Complete resolution of abnormalities was not considered a practical end point because most patients (18/22) had some residual abnormalities. Complete resolution was confirmed in all study patients except 1 who received corticosteroids alone, from whom no convalescent serum sample was obtained. Treatment subgroups did not differ in either demographic or clinical features at post–symptom onset day 7 (TABLE). This comparison was made at day 7 because it is 1 day prior to the median start date of interferon alfacon-1 treatment (day 8; range, days 4-10) and frequently approximates the time of peak disease. The 2 concurrent patients in the comparison group who received high-dose steroids were considered for interferon alfacon-1 therapy but one refused and test, respectively. Serial laboratory tests, oxygen saturation, and temperature were plotted for the 2 groups and compared using repeated-measures analysis of variance. Missing data were imputed using the last-value-carried-forward technique. Kaplan-Meier methods were used to analyze time to 50% resolution of peak lung involvement and time to cessation of supplemental oxygen; significance was calculated using the log-rank test. Patients were censored if at the end of follow-up they had not reached the end point. The data set was created and closed prior to any data analysis. Statistical analyses were completed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). P<.05 was considered significant for all analyses.

### RESULTS

#### Patients

The study population included 16 women and 6 men aged 16 to 86 years. SARS-CoV–associated IgG seroconversion was confirmed in all study patients except 1 who received corticosteroids alone, from whom no convalescent serum sample was obtained. Treatment subgroups did not differ in either demographic or clinical features at post–symptom onset day 7 (TABLE). This comparison was made at day 7 because it is 1 day prior to the median start date of interferon alfacon-1 treatment (day 8; range, days 4-10) and frequently approximates the time of peak disease. The 2 concurrent patients in the comparison group who received high-dose steroids were considered for interferon alfacon-1 therapy but one refused and test, respectively. Serial laboratory tests, oxygen saturation, and temperature were plotted for the 2 groups and compared using repeated-measures analysis of variance. Missing data were imputed using the last-value-carried-forward technique. Kaplan-Meier methods were used to analyze time to 50% resolution of peak lung involvement and time to cessation of supplemental oxygen; significance was calculated using the log-rank test. Patients were censored if at the end of follow-up they had not reached the end point. The data set was created and closed prior to any data analysis. Statistical analyses were completed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). P<.05 was considered significant for all analyses.

### TABLE. Patient Characteristics, Day 7 Clinical Findings, and Additional Treatments*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Interferon Alfacon-1 (n = 9)</th>
<th>Corticosteroids Alone (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 (27-56)</td>
<td>42 (16-86)</td>
<td>.79</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>6 (66.7)</td>
<td>10 (76.9)</td>
<td>.66</td>
</tr>
<tr>
<td>Hospital exposure, No. (%)</td>
<td>9 (100)</td>
<td>13 (100)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Health care workers</td>
<td>9 (100)</td>
<td>7 (53.9)</td>
<td>.46</td>
</tr>
<tr>
<td>Comorbid illness, No. (%)</td>
<td>1 (11.1)</td>
<td>1 (7.7)</td>
<td>.66</td>
</tr>
</tbody>
</table>

**Additional treatment**

- Corticosteroids, No. (%)§ 9 (100) 13 (100) >.99
- High-dose methylprednisolone, No. (%)¶ 5 (55.6) 2 (15.4) .08
- Maximum steroid dose, mg 500 (500-500) 70 (40-500) .02
- Intravenous immunoglobulin, No. (%) 1 (11.1) 1 (7.7) .90
- Antibiotics, No. (%)§ 7 (77.8) 3 (33.3)¶ .13

**Findings from postonset day 7**

- **Maximum temperature, °C** 38.8 (36.8-39.8) 38.4 (36.5-40) .43
- **O₂ saturation, %** 95 (92-99) 93 (92-97) .17
- **Abnormal chest radiograph, No. (%)** 9 (100) 13 (100) >.99
- **Lung involvement, %** 20 (5-70) 20 (10-75) .81
- **Lymphocytes, cells/µL** 800 (400-1290) 840 (440-1680) .57
- **Neutrophils, cells/µL** 2980 (1260-8160) 5640 (2005-9210) .18
- **Platelets, x 10⁹/µL** 183 (125-265) 178 (123-404) .71
- **Lactate dehydrogenase, U/L** 289 (154-721) 317 (161-883) .72
- **Creatine kinase, U/L** 102 (52-328) 140 (55-771) .32
- **Aspartate aminotransferase, U/L** 32 (23-123) 36 (20-121) .94
- **Creatinine, mg/dL** 0.66 (0.48-0.81) 0.65 (0.52-0.97) .65

*SI conversion factor: To convert creatinine to µmol/L, multiply by 88.4.

*Data are expressed as median (range) unless otherwise indicated.

†P values were estimated by the Wilcoxon rank sum test and, for all categorical data, by the Fisher exact test.

‡Comorbid illnesses included 1 patient with hypertension in each group. There was no incidence of diabetes, cancer, or chronic obstructive pulmonary disease.

§Prednisone and methylprednisolone were tapered.

¶High-dose methylprednisolone was started at 500 mg/d for 3 days then tapered; see “Methods” section of text for details.

¶Data available for only 9 patients.
the other was late in the course of disease. The latter patient was transferred from another Toronto hospital and had received intravenous ribavirin, 400 mg every 8 hours, at that hospital for 3 days. Ribavirin was discontinued on admission to NYGH and this patient was intubated and received high-dose methylprednisolone.

**Clinical Course and Adverse Events**

Of the 13 patients treated with corticosteroids alone, 5 (38.5%) were transferred to the ICU, 3 (23.1%) required intubation and mechanical ventilation, and 1 (7.7%) died. Two patients were transferred to the ICU on days 5 and 10 after disease onset and remained in the ICU for 2 and 3 days, respectively. The former patient subsequently died. The other 3 patients were transferred on days 8, 10, and 12 after disease onset and remained there for 10, 14, and 14 days, respectively. These 3 patients were intubated for 9, 5, and 12 days, respectively. These 3 patients were intubated and received high-dose methylprednisolone.

Of the 9 patients treated with interferon alfacon-1, 3 (33.3%) were transferred to the ICU, 1 (11.1%) subsequently required intubation and mechanical ventilation, and none died. Of these patients, 1 who started interferon alfacon-1 on day 8 after disease onset was transferred to the ICU on day 9 and released from the ICU within 24 hours. A second patient received interferon alfacon-1 on day 6 and was transferred to the ICU on day 6, remaining there for 6 days. These 2 patients did not require intubation or ventilation. The third patient started interferon alfacon-1 on day 8 after disease onset, was transferred to the ICU on day 9, was intubated for 14 days, and remained in the ICU for a total of 17 days.

Length of time to discharge was not included as a study outcome because patients receiving interferon alfacon-1 were kept in the hospital for monitoring for the duration of therapy, regardless of clinical status. Patients tolerated interferon alfacon-1 treatment well, with minimal adverse events. The single clinical adverse event reported was fever, which led to discontinuation of the drug in 1 patient. The fever persisted for 1 week after drug discontinuation and was likely due to the underlying disease. None of the patients receiving interferon alfacon-1 developed flulike symptoms, myalgias, or depression. One patient experienced neutropenia with an absolute neutrophil count (ANC) of less than 1000/µL on the last day of treatment. Interferon alfacon-1 was generally associated with a minor transient decrease in ANC (Figure 1A) and elevation of serum transaminase levels (Figure 1D), both of which resolved within 1 to 2 days of drug discontinuation and appeared to be of no clinical consequence. Decreases in ANC and increases in serum transaminase levels are frequently observed in patients with chronic hepatitis C who are receiving interferon therapy.24,25

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**Figure 1. Mean Laboratory Test Result Values**

<table>
<thead>
<tr>
<th>A</th>
<th>Absolute Neutrophil Count</th>
<th>Start of Interferon Alfacon-1 Treatment</th>
</tr>
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<tbody>
<tr>
<td>B</td>
<td>Absolute Lymphocyte Count</td>
<td>Start of Interferon Alfacon-1 Treatment</td>
</tr>
<tr>
<td>C</td>
<td>Platelet Count</td>
<td>Start of Interferon Alfacon-1 Treatment</td>
</tr>
<tr>
<td>D</td>
<td>ALT</td>
<td>Start of Interferon Alfacon-1 Treatment</td>
</tr>
<tr>
<td>E</td>
<td>LDH</td>
<td>Start of Interferon Alfacon-1 Treatment</td>
</tr>
<tr>
<td>F</td>
<td>Creatine Kinase</td>
<td>Start of Interferon Alfacon-1 Treatment</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase; LDH, lactate dehydrogenase. Error bars indicate standard errors. The median interferon alfacon-1 treatment start date was post–symptom onset day 8 (indicated by square; range, days 4–10).

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Follow-up of the 9 interferon alfacon-1 patients to day 60 revealed no evidence of rebound fever or recurrent disease. There was no worsening on chest radiographs, no requirement for supplemental oxygen, and no rehospitalization after cessation of interferon alfacon-1 therapy.

Changes in Clinical Indices
The data in Figure 1 and Figure 2 record the changes in mean values of specific clinical measurements and laboratory test results, obtained for both the interferon alfacon-1 and comparison groups over the course of disease. Analysis of these data with the last-value-carried-forward method and with no data imputation yielded identical results. Time-course plots for mean hemoglobin, calcium, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and creatinine values remained within normal range and were similar among all patients (data not shown). The time course for resolution of fever during the course of disease was indistinguishable between the interferon alfacon-1 and comparison groups (Figure 2A).

As in other studies, lymphopenia was observed in all patients.23,26,27 However, the absolute lymphocyte counts were indistinguishable between the 2 groups and returned to normal levels during the course of disease (Figure 1B). The ANC increased in the comparison group (Figure 1A) and initially in the interferon alfacon-1 group. However, continued interferon alfacon-1 treatment was associated with a decrease in ANC that improved after the drug was discontinued. The interferon alfacon-1–treated group also showed less thrombocytosis during recovery than the comparison group (Figure 1C), possibly because of myelosuppression.

Elevated lactate dehydrogenase (LDH) is a consistent laboratory feature of SARS6,28 and may represent a marker for lung parenchymal damage. Lactate dehydrogenase increased over time in all patients, but a trend toward faster normalization appeared in the interferon alfacon-1 group (Figure 1E). Creatine kinase (CK) levels, which were highly elevated in the comparison group during the mid course of disease, were minimally altered during the entire course of disease in the interferon alfacon-1–treated patients (P = .03 by repeated-measures analysis of variance) (Figure 1F).

Radiographic and Oxygenation Findings
The initial chest radiographs were obtained 3 to 12 days (median, 3 days) and the final radiographs were obtained 7 to 50 days (median, 21 days) after symptom onset. The median number of radiographs obtained per patient was similar in the 2 groups: 11 (range, 7-12) for interferon alfacon-1 patients and 9 (range, 3-12) for the comparison group. The median number of days to peak abnormalities for all patients was 10, with no difference between the interferon alfacon-1 group (median, 11 days; range, 9-12 days) and comparison group (median, 10 days; range, 6-14 days). The median time from peak chest radiographic abnormalities to 50% improvement for interferon alfacon-1 patients was 4 days (range, 2-5 days) and for patients receiving corticosteroids alone was 9 days (range, 4-12 days) (P = .001 by log-rank test) (Figure 3A).

Consistent with these findings, higher oxygen saturation levels were observed in interferon alfacon-1 patients compared with the comparison group (Figure 2B) (P = .02 by repeated-measures analysis of variance). The need for supplemental oxygen resolved significantly faster in interferon alfacon-1 patients than in the comparison group (median, 10 days [range, 0-17 days] vs 16 days [range, 0-21 days]; P = .02 by log-rank test). Fifty percent of patients in the comparison group were still receiving supplemental oxygen by day 21, while none of the interferon alfacon-1 patients required oxygen beyond day 17 (Figure 3B).

COMMENT
This article reports the clinical features and outcomes observed in a SARS patient cohort treated with corticosteroids alone or in combination with interferon alfacon-1. These preliminary findings suggest that treatment with interferon alfacon-1 and steroids was associated with more rapid resolution of radiographic lung abnormalities and better oxygen saturation levels than treatment with corticosteroids alone. In addition, in contrast with this comparison group, in whom the disease was associated with considerable increases in CK and LDH levels, interferon alfacon-1 patients showed less increases in CK levels and a more rapid return of LDH to normal levels. As morbidity and mortality in SARS are directly related to pulmonary space infiltration and LDH and CK levels are thought to represent indicators of lung parenchymal damage, the findings of these preliminary observations are particularly encouraging.
damage and poor prognosis, respectively, 21,23,27 these findings provide preliminary evidence that interferon alfacon-1 therapy may help ameliorate lung parenchymal disease in SARS.

Interferon alfacon-1 therapy was well tolerated by SARS patients and, at least in the group studied herein, did not induce increases in headache, fever, chills, or myalgia—adverse events reported with interferon treatment in other clinical settings. 29 The lack of these adverse events is likely due to the concurrent use of steroids in the patient population in this study. Although interferon alfacon-1 therapy was associated with mild neutropenia and some elevation of serum transaminase levels, these changes were clinically insignificant and resolved with drug discontinuation.

The current study was undertaken for the purpose of providing preliminary data on the tolerability, safety, and potential therapeutic benefit of interferon alfacon-1 in SARS patients when administered in combination with corticosteroids. Although steroid use at high or low doses does not appear to induce severe complications in SARS patients, it is currently unclear whether disease course or outcomes are significantly altered by it. However, to conform to the standard of care, corticosteroid treatment was administered in all study patients. The findings of improved resolution of radiographic abnormalities, higher oxygen saturation, and reduced CK elevation in interferon alfacon-1 patients cannot, therefore, be attributed solely to interferon alfacon-1, independent of corticosteroids. Emerging data suggest that the clinical progression of SARS involves an initial phase when viral replication contributes to the cytolytic damage and immunopathological response, followed by pathological lung damage caused by an overexuberant host immune response. 23 Interferon alfacon-1 may effectively limit viral load, thereby decreasing the subsequent immunopathological damage. Moreover, interferon alfacon-1 may act synergistically with steroids to immunosuppress the host response.

The dosage of interferon alfacon-1 used in this study was selected in consideration of SARS as an acute viral infection and the consequent aim of achieving high enough interferon alfacon-1 levels to effect viral clearance. Data from studies of patients with hepatitis C treated with interferon alfacon-1 have revealed that daily dosing at 9 µg provides a sustained antiviral response 21,29 and that effectiveness in terms of viral clearance increases with 15-µg and 30-µg doses. 30 It is in this context that the 9-µg and 15-µg doses were used in the current study. The 15-µg dose appeared to be well tolerated and may prove to be the more appropriate dose to use in SARS treatment. The optimal dose, as well as the effect of monotherapy with interferon alfacon-1 in the absence of steroids for the management of SARS, needs to be further evaluated in clinical studies.

Furthermore, the findings reported herein need to be cautiously interpreted in view of lack of randomization, the retrospective study design, and limited sample size. However, despite the limitations of this open-label, uncontrolled study, these data suggest that interferon alfacon-1 may be of value in the treatment of SARS and indicate that its use for this purpose merits further evaluation. To this end, a protocol for a randomized controlled clinical trial, the primary objective of which is to evaluate the safety and virologic efficacy of interferon alfacon-1 in the treatment of probable and suspected SARS cases compared with observation and supportive therapy, has been submitted to and approved by Health Canada.

Author Contributions: Dr Fish had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Loutfy, Blatt, Fish. Acquisition of data: Loutfy, Blatt, Siminovitch, Ward, 2003 American Medical Association. All rights reserved.
INTERFERON ALFACON-1 PLUS CORTICOSTEROIDS FOR SARS

Wolff, Lho, Deif, LaMere, Chang, Kain, Faracas, Ferguson, Latchford, Lai, Fish. Analysis and interpretation of data: Loutfy, Blatt, Siminovitch, Ward, Pham, Deif, Lai, Fish. Drafting of the manuscript: Loutfy, Blatt, Siminovitch, Ward, Wolff, Lho, Pham, Deif, Chang, Kain, Latchford, Dennis, Lai, Fish.

Critical revision of the manuscript for important intellectual content: Loutfy, Blatt, Siminovitch, Fish. Statistical expertise: Loutfy, Blatt, Fish. Obtained funding: Siminovitch, Dennis, Fish. Administrative, technical, or material support: Blatt, Siminovitch, Ward, Lho, Pham, Deif, LaMere, Chang, Kain, Faracas, Ferguson, Latchford, Fish.

Study supervision: Loutfy, Blatt, Fish.

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REFERENCES


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