HYponatremia is the most common electrolyte abnormality in the inpatient and outpatient setting. Hyponatremic encephalopathy is the most serious complication of hyponatremia. Significant risk factors for developing hyponatremic encephalopathy include female sex, hypoxia, and underlying central nervous system disease. The symptoms of hyponatremic encephalopathy are largely related to cerebral edema. Hyponatremic encephalopathy constitutes a medical emergency because it might lead to death or permanent neurologic deterioration due to transtentorial herniation or respiratory arrest if untreated.

According to the recent European Clinical Practice Guidelines, hypertonic saline solution is recommended for the treatment of hyponatremic encephalopathy regardless of whether it is acute or chronic. They acknowledge that “the body of evidence to base recommendations on this topic was limited.” The guidelines’ recommendation for hypertonic saline solution were based on 9 case series that varied widely in regard to the setting, symptoms, severity, duration, and therapy used to treat hyponatremic encephalopathy. According to the guidelines, most case reports used a total of 500 mL of 3% sodium chloride solution. The guidelines recommend using repeated 150-mL boluses of hypertonic saline solution, but they acknowledge that “there is no...
evidence in published research to support this assertion. In this article, we evaluated the efficacy and safety of a uniform treatment protocol of 500 mL of 3% sodium chloride solution infused over 6 hours for the management of hyponatremic encephalopathy in the emergency department.

METHODS

Study Participants

This study was conducted from January 1, 1996, through July 1, 2007, in patients older than 18 years presenting to the emergency department at Hospital Professor Alejandro Posadas in Buenos Aires, Argentina, with symptoms of hyponatremic encephalopathy. Patients with hyponatremic encephalopathy were treated with 3% sodium chloride solution according to a protocol recommended by the Argentinian Society of Critical Care Medicine. The protocol consisted of intravenous infusion of 500 mL of 3% sodium chloride solution administered over 6 hours through a large-bore intravenous cannula in conjunction with fluid restriction. Patients were eligible for the hypertonic saline solution protocol if they had serum sodium levels < 130 mEq/L with advanced signs of hyponatremic encephalopathy, such as headache, nausea, vomiting, mental status changes, delirium, confusion, stupor, tremor, asterixis, seizures, respiratory arrest, noncardiogenic pulmonary edema, or other evidence of increased intracranial pressure without other apparent cause. Patients were not candidates for this hypertonic saline solution protocol if they had overt hypovolemic hyponatremia, hypervolemic hyponatremia, chronic kidney disease (CKD) stage 5, or pseudohyponatremia or were having a spontaneous free-water diuresis following the administration of saline solution.

Therapy was initiated in the emergency department within the first few hours of presentation in all patients. All patients received a total of 500 mL of 3% sodium chloride solution over a 6-hour period. Fluid restriction was instituted following the hypertonic saline solution infusion, with further therapy directed in consultation with the nephrology service. Baseline blood chemistry values were obtained prior to the administration of 3% sodium chloride solution, and serum sodium samples were drawn according to protocol at 3, 12, 24, and 48 hours, or more often at the physician’s discretion. An arterial blood gas PaO₂ was recorded when available. Patient demographics, baseline serum chemistry test results, clinical symptoms of hyponatremia, and their duration were recorded. The comorbid conditions assessed were diabetes mellitus, HIV (human immunodeficiency virus) infection, a history of compulsive or uncontrolled alcohol use (alcoholism), chronic obstructive pulmonary disease, CKD stage 3 or 4, hypertension, left ventricular dysfunction, a history of tobacco use (smoking), cerebrovascular accident, acute myocardial infarction, an active neoplasm (cancer), and hypokalemia (potassium < 3.5 mEq/L). Kidney function was assessed at the time of hospital admission with serum creatinine level. The CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used to calculate estimated glomerular filtration rate. Patients were monitored monthly for 6 months following the episode of hyponatremic encephalopathy in order to assess adverse outcomes, including mortality and neurologic impairment.

All patients who received the hypertonic saline solution protocol were included in the study. Subsequent episodes of hyponatremic encephalopathy were included if the episode occurred more than 6 months after the previous episode following complete neurologic recovery. The study was approved by the Institutional Review Board of the Hospital Professor Alejandro Posadas.

Statistical Analysis

All data are expressed as mean ± standard error of the mean, median, or proportions as appropriate. The Kolmogorov-Smirnov test was used to verify the normality of the study variables. Patients with a poor outcome (death or major neurologic sequelae) were compared with those without.

The Kruskal-Wallis or nonparametric Friedman 1-way analysis of variance (ANOVA) was used to compare groups, and repeated-measures ANOVA was used to evaluate changes in serum sodium concentrations within the first 48 hours postadmission. Fisher exact test was used for comparison of count variables. A univariate logistic regression analysis was carried out on the first episode of hyponatremic encephalopathy to determine whether death or neurologic sequelae was a dependent variable on the following potential covariates: sex, age, hypertension, diabetes, left ventricular dysfunction, CKD, hypokalemia, alcoholism, or cancer. Odds ratios with the appropriate 2-sided 95% confidence intervals were reported. All tests were 2 sided, and P < 0.05 was considered statistically significant. The analysis was conducted with SPSS, version 19.0, statistical software (IBM).

RESULTS

Study Participants

There were 71 episodes of hyponatremic encephalopathy in 64 individuals, with 58 individuals having 1 episode each, 5 individuals having 2 each, and 1 individual having 3 episodes of hyponatremic encephalopathy. Twenty-nine individuals presented with seizure activity, 10 were stuporous, 5 were comatose, and 2 had neurogenic pulmonary edema. Patient demographics are reported in Table 1. There was equal distribution of men and women, and most (72%) patients were 65 years or older. The main causes of hyponatremia were syndrome of inappropriate secretion of antidiuretic hormone (SIADH; n = 39 [61%]), thiazide diuretics (hydrochlorothiazide; n = 22 [34%]), and severe symptomatic hypothyroidism (n = 3 [5%]).

Comorbid conditions were present in 56 of 64 (88%) individuals. The most common comorbid conditions were hypertension (n = 45 [70%]), a history of left ventricular dysfunction (n = 23 [36%]), diabetes (n = 14 [22%]), smoking (n = 13 [20%]), and cancer (n = 10 [16%]). Four individuals had a history of alcoholism.

Patient Outcome

All individuals experienced symptoms attributable to hyponatremic encephalopathy, which ranged in duration from 4 hours to 15 days (median, 48 hours) prior to admission. Seventy-five percent presented to medical attention within 72 hours of the first symptom of hyponatremic encephalopathy. Baseline serum sodium level for the 71 episodes of hyponatremic encephalopathy was 114.1 ± 0.8 mEq/L and increased to 117.9 ± 1.3, 121.2 ± 1.2, 123.9 ± 1.0, and 128.3 ± 0.8 mEq/L at 3, 12, 24, and 48 hours following the initiation of 3% sodium chloride...
solution treatment, respectively. The increase in serum sodium level in response to 3% sodium chloride solution is shown in Fig 1. There was no significant difference in serum sodium concentrations during the first 48 hours of therapy between patients with and without adverse outcome or those with and without SIADH. Five individuals had significant overcorrection of hyponatremia, with change in serum sodium level $\geq 25$ mEq/L 48 hours after admission (change in serum sodium level range, 25-32 mEq/L). The cause of hyponatremia was related to the use of thiazide diuretics in 3 and SIADH in 2 of these individuals, 2 of whom additionally had severe hypokalemia (potassium, 1.2 and 2.7 mEq/L). Desmopressin acetate was not used in any patient to prevent overcorrection of hyponatremia. No patient developed neurologic symptoms consistent with cerebrodemyelination.

There was marked improvement in central nervous system symptoms within a few hours of initiation of treatment with 3% sodium chloride solution in 69 of 71 (97%) treated episodes, with complete neurologic recovery at 48 hours following the initiation of treatment. Two patients (Table 2; patients 2 and 7) did not respond to therapy and had permanent neurologic deficit. Fourteen (23%) individuals had adverse outcomes (Table 2), with 12 deaths and 2 patients having a permanent neurologic deficit. All adverse outcomes occurred following a single episode of hyponatremic encephalopathy. All 12 deaths occurred from causes unrelated to hyponatremia following the correction of

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**Table 1.** Demographics and Comorbid Conditions of Participants Having Hyponatremic Encephalopathy at Initial Presentation by Baseline Serum Sodium Tertiles

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall (n = 64)</th>
<th>Na = 102-110 mEq/L (n = 22)</th>
<th>Na = 111-117 mEq/L (n = 21)</th>
<th>Na = 118-126 mEq/L (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>68.0 ± 2.0</td>
<td>71.7 ± 3.3</td>
<td>65.1 ± 3.8</td>
<td>66.9 ± 3.3</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>30/34</td>
<td>8/14</td>
<td>10/11</td>
<td>12/9</td>
</tr>
<tr>
<td>Symptom duration preadmission (h)</td>
<td>85.3 ± 9.2</td>
<td>72.7 ± 12.8</td>
<td>88.4 ± 18.5</td>
<td>84.2 ± 19.5</td>
</tr>
</tbody>
</table>

**Causes of hyponatremia**

- SIADH: 39, 12, 12, 15
- Thiazides: 22, 9, 9, 4
- Hypothyroidism: 3, 1, 0, 2

**Lab values**

<table>
<thead>
<tr>
<th>Creatinine (mg/dL)</th>
<th>0.93 ± 0.05</th>
<th>0.91 ± 0.07</th>
<th>0.92 ± 0.06</th>
<th>0.97 ± 0.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>113.8 ± 0.8</td>
<td>106.3 ± 0.6</td>
<td>114.5 ± 0.4</td>
<td>121.4 ± 0.6</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.1 ± 0.1</td>
<td>4.2 ± 0.2</td>
<td>3.7 ± 0.3</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>79.8 ± 1.3</td>
<td>73.4 ± 1.2</td>
<td>78.5 ± 2.2</td>
<td>87.4 ± 1.4</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>77.8 ± 3.4</td>
<td>74.7 ± 4.7</td>
<td>79.8 ± 5.6</td>
<td>79.2 ± 7.4</td>
</tr>
</tbody>
</table>

**Comorbid conditions**

| Diabetes | 14 | 6 | 4 | 4 |
| HIV      | 3  | 0 | 1 | 2 |
| Alcoholism | 5  | 3 | 2 | 0 |
| COPD     | 3  | 1 | 0 | 2 |
| CKD stages 3 or 4 | 4  | 1 | 1 | 2 |
| Hypertension | 44 | 18 | 12 | 14 |
| LVD      | 22 | 10| 6 | 6 |
| Smoking  | 13 | 4 | 5 | 4 |
| CVA      | 6  | 0 | 1 | 5 |
| Acute MI | 3  | 0 | 2 | 1 |
| Cancer   | 10 | 4 | 3 | 3 |

Median Charlson scorea: 2.0, 2.0, 2.0, 2.0

Note: Values for categorical variables are given as number; values for continuous variables, as mean ± standard error of the mean.

Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; LVD, left ventricular dysfunction; MI, myocardial infarction; Na, sodium; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

aCharlson Comorbidity Index predicts 10-year mortality for a patient who may have a range of comorbid conditions: 0 points (none), 1-2 points (low), 3-4 points (moderate), and >5 points (high).
serum sodium level and subsequent neurologic improvement. Mean survival for the 12 patients who died was 38.5 ± 15 days (Table 2). Male sex and alcoholism were associated with adverse outcome on univariate analysis, whereas hypokalemia and thiazide diuretic use were not (Table 3).

No patient developed neurologic symptoms consistent with cerebral demyelination at any point during the 6-month follow-up period. There also were no complications directly related to the infusion, such as a local infusion reaction, pulmonary edema, or hypertension.

**DISCUSSION**

This article reports a uniform treatment protocol with 500 mL of intravenous 3% sodium chloride solution over 6 hours for the management of hyponatremic encephalopathy. To our knowledge, this is the largest study of its kind evaluating a uniform treatment protocol and the only study with long-term follow-up. This study demonstrated that 3% sodium chloride solution was effective in reversing the symptoms of hyponatremic encephalopathy. There was a favorable response to treatment with 3% sodium chloride solution, with prompt reversal of symptoms of hyponatremic encephalopathy, in 97% of episodes. There were no apparent cases of neurologic injury related to overcorrection of hyponatremia. The hypertonic saline solution was well tolerated through a peripheral vein without reports of phlebitis or tissue necrosis, and there were no episodes of acute hypertension or pulmonary congestion related to the 3% sodium chloride solution infusion.

There were only 2 episodes in which response to therapy may have been inadequate (Table 2; patients 2 and 7). These 2 patients may have experienced long-term neurologic injury attributable to hyponatremic encephalopathy. In both cases, the patients had concomitant hypoxia, which is a known risk factor for brain damage. These 2 patients also had insufficient correction of hyponatremia because the absolute change in serum sodium level was only 2 to 3 mEq/L at 12 hours and 7 mEq/L at 48 hours. These 2 patients did not have the expected increase in serum sodium levels that would be predicted after receiving 3% sodium chloride solution. Both patients had SIADH, and it is known that the response to therapy can be less than expected due to concentrated and hypertonic urine. It also is possible that these individuals had larger than expected total-body water, which may have contributed to a less than predicted response to therapy. These 2 patients likely would have benefited from either a larger quantity of 3% sodium chloride solution or additional therapy to antagonize the renal concentration and promote urinary free-water loss, such as a loop diuretic or V2 antagonist.

The overall mortality rate for the study was 19%, which is similar to most other reports in the literature. All deaths occurred after correction of hyponatremia and resolution of neurologic symptoms. None of the deaths could be attributed directly to hyponatremia. Only male sex and alcoholism were associated with death or poor neurologic outcome following univariate analysis. Alcoholism is a well-recognized risk factor for developing cerebral demyelination following the correction of hyponatremia, yet none of the patients appeared to develop symptoms consistent with this.

All deaths were unrelated to hyponatremic encephalopathy (Table 2) and primarily were due to sepsis, as has been reported by others. Numerous studies have demonstrated that hyponatremia is an independent risk factor for mortality. The reasons for this are not entirely clear, but some insights into the potential mechanism are evolving. It now is recognized that even mild levels of chronic hyponatremia cause subtle cognitive impairment. It also is known that hyponatremia affects bone metabolism and leads to bone demineralization. Recent studies have shown that sodium balance plays an important role in immunity, with a hypertonic interstitial water content being necessary for lymphoid tissue to mount an immune response. This may help explain why sepsis is a frequent cause of death in patients with hyponatremia. For these reasons, hyponatremia could adversely affect outcome independent of hyponatremic encephalopathy, and treatment in theory could improve outcome.

Since embarking on this study, we proposed the use of the intermittent 100-mL 3% sodium chloride...
### Table 2. Main Characteristics of Patients With Hyponatremic Encephalopathy Having an Adverse Outcome

| Pt No. | Sex | Age (y) | Cause                          | Comorbid Conditions | Symptom Duration Preadmission (h) | Charlson Score<sup>a</sup> | Scr (mg/dL) 12 h | eGFR (mL/min/1.73 m<sup>2</sup>) Baseline | Serum Na (mEq/L) | ΔNa<sup>b</sup> (mEq/L) Baseline Serum K (mEq/L) | Pao<sub>2</sub> at Admission (mm Hg) | Symptoms Resolved<sup>c</sup> | Survival (d) | Final Event | Outcome |
|--------|-----|---------|-------------------------------|---------------------|----------------------------------|---------------------|----------------|---------------------------------|----------------|-----------------------------------|------------------------|-------------------|-------------|-----------|
| 1      | F   | 82      | HypoT COPD, HTN, CVA          |                     | 72                               | 6                   | 2.0            | 22.7                                          | 124             | 126                              | 129                    | 4.2               | 52         | Yes       | 18       | Arrhythmia | Death     |
| 2      | M   | 76      | SIADH CVA                      |                     | 48                               | 2                   | 1.1            | 64.9                                          | 120             | 123                              | 127                    | 5.3               | 57         | No        | Brain damage | Neurologic deficit |
| 3      | M   | 55      | SIADH Alcoholism, HTN          |                     | 72                               | 2                   | 0.7            | 106.2                                         | 107             | 110                              | 125                    | 3.9               | NA         | Yes       | 11       | Sepsis     | Death     |
| 4      | M   | 55      | SIADH DM, COPD, HTN, CVA, cancer |                 | 48                               | 12                  | 0.8            | 100.6                                         | 121             | 127                              | 131                    | 4.6               | NA         | Yes       | 4        | Sepsis     | Death     |
| 5      | M   | 42      | SIADH HIV                      |                     | 96                               | 6                   | 0.6            | 124.0                                         | 118             | 121                              | 121                    | 5.4               | NA         | Yes       | 11       | Sepsis     | Death     |
| 6      | M   | 79      | SIADH HTN, LVD                 |                     | 48                               | 2                   | 0.6            | 95.6                                          | 104             | 113                              | 117                    | 24                | NA         | 43        | Yes       | 130       | Sepsis     | Death     |
| 7      | M   | 85      | SIADH None                     |                     | 24                               | 0                   | 0.6            | 91.7                                          | 128             | 131                              | 133                    | 7                 | NA         | 69        | No        | Brain damage | Neurologic deficit |
| 8      | M   | 65      | SIADH Alcoholism               |                     | NA                               | 3                   | 0.6            | 105.5                                         | 114             | 124                              | 128                    | 133               | 19        | NA         | 15       | Sepsis     | Death     |
| 9      | M   | 56      | SIADH None                     |                     | NA                               | 0                   | 0.4            | 132.8                                         | 119             | 120                              | 121                    | 2                 | 4.6        | 91        | Yes       | 5         | Sepsis     | Death     |
| 10     | M   | 29      | SIADH Alcoholism               |                     | NA                               | 1                   | 0.6            | 135.9                                         | 116             | 131                              | 141                    | 25                | 2.7        | NA         | 135      | Sepsis     | Death     |
| 11     | F   | 75      | SIADH LVD, HTN                 |                     | 14                               | 2                   | 1.0            | 55.2                                          | 103             | 111                              | 115                    | 23                | 5.9        | NA         | 6        | Arrhythmia | Death     |
| 12     | F   | 77      | HCTZ CKD, HTN                  |                     | 168                              | 3                   | 2.3            | 19.9                                          | 104             | 109                              | 111                    | 18                | 5.7        | 98        | Yes       | 21        | Sepsis     | Death     |
| 13     | M   | 65      | SIADH Alcoholism               |                     | NA                               | 1                   | 0.6            | 105.5                                         | 111             | 114                              | 116                    | 14                | 3.4        | 99        | Yes       | 136       | Sepsis     | Death     |
| 14     | M   | 77      | SIADH DM, cancer               |                     | 24                               | 10                  | 1.3            | 52.6                                          | 116             | 120                              | 124                    | 130               | 14        | NA         | 87        | Yes       | 10        | Arrhythmia | Death     |
|       |     |         |                               |                     | 65.5±                           |                     | 3.57±          | 0.94±                                         | 86.7±           | 114.5±                          | 119.7±                  | 122.7±                     | 127.6±            | 4.4±             | 74±        | 38.6±      | 4.4±      | 15.1±      | 15.1±      |

**Note:** Conversion factor for Scr in mg/dL to μmol/L, ×88.4.

Abbreviations and definitions: Adverse outcome, death or permanent neurologic deficit; CKD, chronic kidney disease stage 3 or 4; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; HIV, human immunodeficiency virus; HTN, hypertension; HypoT, hypothyroidism; K, potassium; LVD, left ventricular dysfunction; Na, sodium; NA, not available; Pt, patient; Scr, serum creatinine; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

<sup>a</sup>Charlson Comorbidity Index predicts 10-year mortality for a patient who may have a range of comorbid conditions: 0 points (none), 1-2 points (low), 3-4 points (moderate), and ≥5 points (high).

<sup>b</sup>Change in serum sodium level from baseline to the 48-hour time point.

<sup>c</sup>Resolution of hyponatremic symptoms.

<sup>d</sup>Mean ± standard error of the mean of all cases.
solution bolus to treat hyponatremic encephalopathy. However, this approach has yet to be validated in large-scale studies. A similar approach has since been adopted by 3 European societies, representing intensive care medicine, endocrinology, and nephrology, when they convened and published clinical practice guidelines in 2014 on the diagnosis and treatment of hyponatremia. They recommend treating hyponatremic encephalopathy with moderate to severe symptoms, whether acute or chronic, by administering 3 consecutive 150-mL boluses of 3% sodium chloride solution over 20 minutes each or until a target of a 5-mEq/L increase in serum sodium concentration in 1 hour is achieved. Those recommendations are based largely on 9 case series reporting on the use of hypertonic saline solution as treatment for hyponatremic encephalopathy. Those series varied widely in regard to the setting, symptoms, severity, duration, and therapy used. The total amount of 3% sodium chloride solution administered in this study is similar to the total volume recommended in the European guidelines, and the average change in serum sodium level at 12 hours of 7 mEq/L is in keeping with their recommendations.

One of the main concerns with treating severe chronic hyponatremia is the potential for developing cerebral demyelination. Animal studies have demonstrated that large and abrupt increases in serum sodium levels in chronically hyponatremic animals results in astrocytic injury and subsequent demyelination. Humans rarely undergo the large changes in serum sodium levels that are generated in laboratory animals, but they frequently are subject to numerous other risk factors for demyelination that these animals are not, such as hypoxia, hypokalemia, hypophosphatemia, malnutrition, and liver disease. This makes it difficult to determine the relationship between change in serum sodium level and demyelination in humans. We did not find clinical evidence of cerebral demyelination, but this case series may have been too small to detect this rare potential complication of chronic hyponatremia.

One of the limitations of this study is that it neither was a randomized trial nor had different treatment arms or a comparison. This study was not randomized because it would be unethical to withhold therapy with 3% sodium chloride solution in patients with symptomatic hyponatremia and to treat them with fluid restriction alone. It previously has been demonstrated in a nonrandomized prospective study that fluid restriction alone is ineffective in treating hyponatremic encephalopathy and is associated with high morbidity and mortality. There was no comparison group because intravenous 3% sodium chloride solution is the only accepted treatment for hyponatremic encephalopathy. This study did not have different treatment arms of 3% sodium chloride solution because the primary aim of the study was to establish whether a uniform treatment protocol could be used effectively and safely for the management of hyponatremic encephalopathy, and not to establish the ideal treatment protocol. To our knowledge, there have been no randomized trials evaluating hypertonic saline solution for the management of hyponatremic encephalopathy, and an ideal protocol has not been validated. Other limitations of this study were that it was single center and restricted to patients with outpatient hyponatremia, and the patient population was not ethnically diverse. Therefore, these results may not be generalizable in a different patient population or hospital setting. We also do not have neuroimaging studies to absolutely exclude the development of demyelinating lesions, but the absence of adverse neurologic outcome on long-term follow-up is highly suggestive that there were no clinically significant demyelinating lesions. Given the rarity of cerebral demyelination, the number of cases in this study may have been too small to provide definitive assessment of the safety of this protocol.

In conclusion, this study demonstrates that a uniform treatment protocol with 3% sodium chloride solution is effective in reversing the symptoms of hyponatremic encephalopathy in the emergency department. There were no local reactions or evidence of cerebral demyelination in this relatively small cohort.

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Contributions: Research idea and study design: MLM, JCA, DC. Data acquisition: DC, FB; data analysis/interpretation: MLM, JCA, DC, RH; statistical analysis: RH, CDG, MLM, JCA. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JCA takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

REFERENCES


