Hypokalemia Among Patients Receiving Treatment for Multidrug-Resistant Tuberculosis*

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Introduction: Between January 1999 and December 2000, 125 patients in Lima, Peru were enrolled in individualized treatment for multidrug-resistant tuberculosis (MDR-TB). Hypokalemia was observed to be an important adverse effect encountered in this cohort.

Objective: To identify risk factors associated with the development and persistence of hypokalemia during MDR-TB therapy, and to review the incidence and management of hypokalemia in patients receiving MDR-TB therapy.


Results: Among 115 patients who were screened for electrolyte abnormalities, 31.3% had hypokalemia, defined as a potassium level of < 3.5 mEq/L. Mean serum potassium at time of diagnosis was 2.85 mEq/L. Diagnosis of low serum potassium occurred, on average, after 5.1 months of individualized therapy. Multivariate analysis of risk factors for this adverse reaction identified two causes: administration of capreomycin, and low initial body weight. Normalization of potassium levels was achieved in 86% of patients.

Conclusions: Electrolyte disturbance was frequently encountered in our cohort of patients with MDR-TB. Successful screening and management of hypokalemia was facilitated by training the health-care team in the use of a standardized algorithm. Morbidity from hypokalemia can be significant; however, effective management of this side effect is possible without sacrificing MDR-TB treatment efficacy. (CHEST 2004; 125:974–980)

Key words: capreomycin; electrolyte; hypokalemia; hypomagnesemia; magnesium; multidrug-resistant tuberculosis; potassium; tuberculosis

Abbreviations: CI = confidence interval; DOT = directly observed therapy; MDR-TB = multidrug-resistant tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) remains an international public health threat. Unfortunately, the treatment of MDR-TB, defined as infection with strains of Mycobacterium tuberculosis with resistance to both isoniazid and rifampin, is challenging, with treatment length ranging from 18 to 24 months, including parenteral therapy for a minimum of 6 months. Patients receiving MDR-TB therapy tend to have higher rates of adverse reactions and lower cure rates when compared with those receiving treatment for pansusceptible disease. Yet, effective ambulatory treatment of MDR-TB in resource-poor settings, although difficult, is nonetheless possible. In one community-based treatment project in northern Lima, Peru, > 80% of patients receiving ambulatory individualized therapy for MDR-TB were successfully cured. An important component of the success of this project has been the aggressive management of adverse reactions through a network of health-care workers from the Ministry of Health and Socios En Salud, a nongovernmental organization.

Electrolyte disturbance is one of the most chal-
lenging adverse reactions related to MDR-TB management, in particular because of the paucity of presenting symptoms and potential morbidity associated with this disorder. Reasons for electrolyte disturbance among patients treated for MDR-TB are likely multifactorial. Both potassium and magnesium deficiencies are associated with a number of chronic diseases, such as tuberculosis, malnutrition, alcoholism, and diabetes mellitus. In addition, diarrhea and vomiting caused by antituberculous agents can contribute to GI electrolyte loss.

There is also evidence that the use of aminoglycosides and capreomycin causes renal wasting of electrolytes, including potassium, magnesium, and calcium. Both aminoglycosides and capreomycin are thought to induce secondary hyperaldosteronism leading to urinary loss of potassium and magnesium. Because magnesium serves as a co-factor in the adenosine triphosphatase-dependent mechanism for active transport of sodium and potassium across the cell membrane, further potassium wasting occurs as a consequence of resultant intracellular magnesium deficiency. Lastly, hypomagnesemia can induce hypocalcemia, in part through the suppressive effect of low magnesium levels on the parathyroid hormone.

Electrolyte disturbance has been associated with high cumulative doses of aminoglycosides, in particular with gentamicin. The incidence of electrolyte disorders from aminoglycosides is approximately 4.5%. Electrolyte disturbance, in particular hypokalemia, appears to occur more frequently with capreomycin, and is reported in 4 to 15% of patients receiving capreomycin therapy for 6 to 26 months. Hesling suspected electrolyte disturbances in 5 patients (14.7%) in a cohort of 34 patients, all of whom were all receiving capreomycin. Occurrence did not appear to be related to preexisting renal disease. Death occurred in one patient; pathologic inspection showed nonspecific hydropic changes in the epithelial lining of the distal tubules.

In another study by Aquinas and Citron, a cohort of 40 tuberculosis patients received capreomycin at 15 mg/kg for 6 months. Seven patients were noted to have at least two serum potassium values <3.2 mEq/L. While the association of hypokalemia with capreomycin was unclear in five of these individuals, two patients (5%) had recurrence of hypokalemia on resuming capreomycin, with resolution on discontinuation of the injectable. Interestingly, among the remaining 33 individuals, a statistically significant rise in serum potassium was observed in the second 6 months of treatment vs the first 6 months. The authors postulated that this trend was due to response of tuberculosis to chemotherapy.

Holmes et al observed electrolyte abnormalities in 3 of 67 patients (4.5%) receiving capreomycin. The level of potassium ranged from 2.9 to 3.2 mEq/L, with concomitant hypocalcemia, hypomagnesemia, and a hypochloremic alkalosis. Two patients had received therapy for >20 months, while one patient had been receiving tuberculosis treatment for 6 months.

Electrolyte disturbances may be manifested as minor complaints such as fatigue, cramps, nausea, and irritability, or by serious complications, including tetany, seizures, and lethal cardiac arrhythmias. Given the nonspecific early symptoms and significant morbidity associated with electrolyte wasting, regular monitoring and replacement is critical. While management approaches vary in the literature cited above, correction of electrolyte abnormalities is possible without discontinuation of parenteral therapy, through aggressive repletion of potassium and magnesium. In particular, correction of hypomagnesemia contributes to the normalization of calcium and potassium deficiencies. Indeed, hypokalemia may be refractory to treatment if hypomagnesemia is present and not addressed. Spironolactone (100 to 300 mg/d) may also aid in the normalization of serum potassium and magnesium. Normalization of electrolyte values may take up to 4 months after cessation of the offending agent.

We report here on the incidence of hypokalemia and hypomagnesemia in a cohort of individuals treated for MDR-TB; in particular, we explore the risk factors associated with hypokalemia in our cohort of patients and describe our approach to management.

**Clinical Case**

EB is a 35-year-old man receiving MDR-TB therapy with a regimen of capreomycin, levofloxacin, para-aminosalicylic acid, cycloserine, amoxicillin-clavulanic acid, clarithromycin, and clofazimine. After a month of treatment, routine electrolyte screening revealed a potassium level of 2.7 mEq/L (normal limits, 3.5 to 5.5 mEq/L). Magnesium level was initially within normal limits at 2.3 mEq/L (range, 1.8 to 2.1 mEq/L). The patient denied significant vomiting or diarrhea. He reported mild fatigue and occasional cramping of leg muscles. Figure 1 summarizes the patient’s course, showing the correlation of serum potassium and magnesium with daily supplementation with potassium chloride and magnesium sulfate. After discontinuation of capreomycin in January of 2001, the electrolyte deficiencies resolved and potassium and magnesium supplementation were discontinued within 1 month.
Materials and Methods

Study Population

The cohort included all 125 patients consecutively enrolled in MDR-TB treatment between January 1, 1999, and December 31, 2000. Patients were enrolled throughout metropolitan Lima in all Ministry of Health hospitals, health centers, and health posts offering tuberculosis therapy. All patients received individualized therapy for documented MDR-TB through a collaborative effort of a nongovernmental organization, Socios En Salud; Harvard Medical School; and the Peruvian National Tuberculosis Program.

Treatment Protocol

Patients received directly observed therapy (DOT) delivered in health establishments and in their homes by community health workers. Drug resistance was established by conventional or BACTEC methods (Becton-Dickinson; Sparks, MD) performed by the Massachusetts State Laboratory Institute on sputum specimens. Routine electrolyte (serum potassium and magnesium) monitoring was performed while receiving an injectable agent (i.e., streptomycin, amikacin, kanamycin, or capreomycin). While baseline electrolytes were not universally screened, they were checked in 44 patients (35.2%), and findings were normal in all cases. Of note, beginning in July of 2000, the health-care team—including physicians, nurses, and health promoters—was trained in a protocol for monthly electrolyte and creatinine surveillance and management of electrolyte disturbances. In addition, all patients had monthly evaluations by a physician trained in MDR-TB management, and any individuals reporting symptoms suggestive of electrolyte disturbance underwent further laboratory testing. Potassium and magnesium serum levels were performed by various laboratories, depending on the patient’s residence. All laboratories reported their normal values with the patient’s results. While the lower limit of normal potassium was 3.5 mEq/L, according to all laboratories, the lower limit of normal magnesium varied among the laboratories performing this test (between 1.5 mEq/L and 2.0 mEq/L). Individuals with a diagnosed electrolyte disturbance were managed by health-care providers of Socios En Salud and the Peruvian National Tuberculosis Program.

Study Method

A case series with retrospective chart review was conducted for all 125 patients consecutively enrolled in the DOTS-Plus program between January 1, 1999 and December 31, 2000. All patients had completed at least 16 months of treatment at the time of chart review, unless treatment had been interrupted due to death or default. All charts were reviewed by a clinician experienced in MDR-TB management. Variables extracted from the chart review included the following: age; sex; number of previous treatment regimens; drugs in the individualized regimen; presence of a comorbid condition, including diabetes mellitus, HIV, renal dysfunction and hypothyroidism; and treatment response. All serum potassium and magnesium results, with the date and normal limit of each value, were recorded. Management of electrolyte disturbance was also documented.

Hypokalemia was defined as serum potassium below 3.3 mEq/L and hypomagnesemia as serum magnesium of < 1.5 mEq/L. Electrolyte correction was defined as a normalization of serum potassium or serum magnesium (serum potassium ≥ 3.5, serum magnesium ≥ 1.8), after which all subsequent values remained above these lower limits. Hypothyroidism was defined as a serum thyroid stimulating hormone > 10 IU/mL. Renal dysfunction was defined as two consecutive creatinine values that were elevated > 50% above baseline or nephrotic syndrome as evidenced by > 2 g protein in 24-h urine. Body mass index was calculated by initial body weight in kilograms divided by the square of height in meters. Poor treatment outcome was defined as death, abandonment, treatment failure or, if the patient was still in treatment at the time of analysis, positive sputum culture.

Figure 1. Summary of potassium and magnesium serum levels and supplementation in case example.
results (i.e., any positive culture result within the last two recorded monthly cultures). Conversely, favorable treatment outcome was defined as either cure or, if still in treatment, culture-negative status. Patients were considered to be culture negative if, at the time of analysis, their two most recent monthly culture findings were confirmed negative. Death from all causes was included in death as an outcome.

Statistical Analysis

All data were recorded in Microsoft Excel 98 (Microsoft Corporation; Seattle, WA); all statistical analysis was performed using SAS (version 8.2; SAS Institute; Cary, NC). Reported p values are two-sided Fisher exact tests. Multivariable analysis was performed using logistic regression. Kaplan-Meier estimates, and Cox proportional-hazards models were used to identify variables associated with time to resolution of hypokalemia.

Results

Patient charts were available for all 125 patients; however, electrolyte data were not available for 10 patients. Among these cases, three individuals died within the first month of treatment. Among the remaining seven patients, two individuals were cured at the time of analysis, two were in treatment and culture negative, one died 17 months into individualized therapy, and two defaulted (both in their second month of treatment). Serum electrolyte data were therefore available for 115 of the 125 patients (92%). Subsequent analysis was performed among this cohort of 115 individuals.

Demographic and baseline variables for 115 patients are shown in Table 1. Forty of the 115 patients (34.8%) were found to have an electrolyte disturbance during the course of individualized therapy. Thirty-six patients (31.3%) had hypokalemia, 18 patients (15.7%) had hypomagnesemia, and 14 patients (12.2%) had both low potassium and magnesium. In general, our cohort was young, with a mean age of 30.1 years (range, 11 to 75 years); approximately half of the patients were male, and patients were infected by strains resistant to roughly six drugs. There were no patients with HIV in this cohort.

As shown in Table 1, in a univariate analysis, factors significantly associated with the occurrence of hypokalemia were choice of injectable, hypomagnesemia, hypothyroidism, and low initial weight. These significant variables (capreomycin, initial weight, and hypothyroidism) were included in a multivariable analysis, wherein only capreomycin (p < 0.0001) and initial weight (p = 0.004) were significantly associated with occurrence of hypokalemia, with adjusted hazard ratios of 36.1 (95% confidence interval [CI] 10.10 to 129.57) and 0.93 (95% CI, 0.88 to 0.98), respectively. Of note, among the 44 patients receiving capreomycin, the incidence of hypokalemia was 68.2%. Conversely, use of streptomycin as the choice of injectable was associated with lower rates of hypokalemia; among the 39 individuals who received streptomycin, only 1 patient acquired hypokalemia. Higher mortality rates were observed among those patients with hypokalemia; with a crude

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With Hypokalemia (n = 36)</th>
<th>Without Hypokalemia (n = 79)</th>
<th>p Value</th>
<th>Crude Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.7 ± 10.0</td>
<td>29.3 ± 9.6</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>18 (50.0)</td>
<td>47 (59.5)</td>
<td>0.42</td>
<td>0.89 (0.68–1.14)</td>
</tr>
<tr>
<td>No. of drugs to which strain resistant</td>
<td>5.6 ± 1.6</td>
<td>5.8 ± 1.7</td>
<td>0.38</td>
<td></td>
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<tr>
<td>No. of previous treatments</td>
<td>3.5 ± 1.6</td>
<td>3.5 ± 1.3</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Initial weight, kg</td>
<td>52.2 ± 11.2</td>
<td>58.2 ± 12.1</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>20.2 ± 3.9</td>
<td>21.7 ± 3.8</td>
<td>0.059</td>
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<tr>
<td>Injectable drug</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amikacin</td>
<td>2 (5.6)</td>
<td>1 (1.3)</td>
<td>0.23</td>
<td>2.09 (0.42–10.40)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>30 (83.3)</td>
<td>14 (17.7)</td>
<td>&lt;0.0001</td>
<td>2.88 (1.86–4.46)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>3 (8.3)</td>
<td>26 (32.9)</td>
<td>0.005</td>
<td>0.69 (0.56–0.85)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1 (2.8)</td>
<td>38 (48.1)</td>
<td>&lt;0.0001</td>
<td>0.55 (0.45–0.69)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>14 (38.9)</td>
<td>4 (5.1)</td>
<td>&lt;0.0001</td>
<td>3.48 (1.46–8.31)</td>
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<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
<td>2 (2.5)</td>
<td>1.0</td>
<td>0.68 (0.60–0.77)</td>
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<td>Hypothyroidism</td>
<td>16 (44.4)</td>
<td>17 (21.5)</td>
<td>0.015</td>
<td>1.47 (1.03–2.09)</td>
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<tr>
<td>Renal dysfunction</td>
<td>2 (5.6)</td>
<td>1 (1.3)</td>
<td>0.23</td>
<td>2.09 (0.42–10.40)</td>
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<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Favorable outcome</td>
<td>25 (69.4)</td>
<td>62 (78.5)</td>
<td>0.35</td>
<td>0.85 (0.61–1.18)</td>
</tr>
<tr>
<td>Death</td>
<td>8 (22.2)</td>
<td>8 (10.1)</td>
<td>0.14</td>
<td>1.43 (0.87–2.38)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%).
relative risk of 1.43 (95% CI, 0.87 to 2.38); however, this association was not statistically significant.

At the time of analysis, favorable outcome was observed in 87 patients (75.7%) and poor outcome in 28 patients (24.3%). Among those with favorable outcome, 29 patients (25.2%) were cured and 58 patients (50.4%) were culture negative in treatment. Patients with poor outcome included 16 patients (13.9%) who died, 3 patients (2.6%) who abandoned therapy, and 9 patients (7.8%) who remained culture positive despite at least 16 months of treatment. None were classified as treatment failures.

The mean duration of individualized therapy at the time of diagnosis of hypokalemia was 5.1 months (SD, 4.0). The average potassium was 2.85 mEq/L on presentation, with a nadir of 2.65 mEq/L, occurring approximately 6 weeks after diagnosis of hypokalemia. Approximately 86% of those with hypokalemia went on to normalize, with a mean duration of potassium disturbance of 6.6 months (SD, 3.9). Most individuals with hypokalemia received oral or IV potassium supplementation (88.9%), as well as oral or IV magnesium (86.1%); in addition, approximately 36% received amiloride (at doses of 12.5 to 50 mg/d).

Given the association of higher mortality associated with hypokalemia, we further examined the relationship between hypokalemia and death. In a univariate analysis among those with hypokalemia, the only factor significantly associated with higher mortality was lack of resolution of hypokalemia (p = 0.0004). We subsequently analyzed factors associated with time to resolution of hypokalemia. In a multivariable model, factors associated with earlier time to resolution were male gender (adjusted hazard ratio, 3.56 [95% CI, 1.49 to 8.51]) and absence of hypomagnesemia (adjusted hazard ratio, 0.46 [95% CI, 0.21 to 0.998]); the effect of hypomagnesemia is demonstrated in the Kaplan-Meier curves shown in Figure 2.

We also assessed the effect of implementing a protocol for routine electrolyte surveillance. Prior to August 1, 2000, electrolytes were monitored in 66 of 75 individuals (88%). In contrast, electrolytes were monitored in 49 of all 50 individuals (98.0%) enrolled from August 1, 2000, to December 31, 2000. While the use of capreomycin decreased (44% among the early cohort vs 22% among the late cohort), the rates of hypokalemia among those receiving capreomycin remained fairly constant (69.7% vs 63.6%). The value of the initial low potassium was similar (2.9 vs 3.0), but diagnoses were made earlier after our programmatic intervention (5.3 vs 2.4 months, p = 0.053). In addition, hypokalemia was corrected in 100% of all individuals after the intervention (vs 87.0 in the earlier group). While these changes were not statistically significant in this univariate analysis, the implementation of a program-wide protocol appeared to shorten the time to diagnosis of hypokalemia and improve rates of electrolyte resolution.

**DISCUSSION**

Hypokalemia and hypomagnesemia are important adverse reactions of MDR-TB therapy, particularly among patients receiving capreomycin. We describe here a high incidence of electrolyte disorders in the
outcome. The association of hypomagnesemia with gender with poor MDR-TB treatment was also observed in the assessed in this analysis impacts the outcome of possible that some biological or social factor not line rates of electrolyte disturbances, it is also reasonable alternative.

In our cohort, use of capreomycin and low initial body weight were associated with an increased likelihood of acquiring hypokalemia. While we would recommend screening all patients receiving injectable therapy on a monthly basis, it may be prudent to monitor individuals with low body weight more closely. In addition, even though continuation of capreomycin is often necessary (used in our cohort for individuals with resistance to all aminoglycosides), malnutrition may be a correctable risk factor for electrolyte disturbance.

Hypomagnesemia often accompanied hypokalemia and was likely induced by the same mechanism of electrolyte wasting. Since magnesium deficiencies presented on average 2.7 months after diagnosis of hypokalemia, we have concluded that monitoring serum potassium alone is sufficient to monitor for electrolyte abnormalities. Serum magnesium and calcium levels may be checked in hypokalemic and/or symptomatic individuals. In areas where serum magnesium and/or calcium levels are not available, empiric repletion of magnesium and calcium is a reasonable alternative.

Even more interesting are the effects of gender and magnesium deficiency on time to correction of hypokalemia. While women may have higher baseline rates of electrolyte disturbances, it is also possible that some biological or social factor not assessed in this analysis impacts the outcome of women. This phenomenon was also observed in the association of gender with poor MDR-TB treatment outcome. The association of hypomagnesemia with refractory hypokalemia, however, has been well described and suggests a role for empiric magnesium supplementation in all patients identified with low potassium. In addition, the poor correlation between serum and total-body magnesium also justifies empiric, instead of sliding-scale, magnesium repletion.

Once diagnosed, a staged approach to electrolyte management is reasonable. Contributing factors to electrolyte disturbance—such as vomiting, diarrhea, and dehydration—should be addressed. In general, potassium supplementation is provided if the serum potassium is < 3.5 mEq/L. In our program, patients usually receive electrolyte repletion on an ambulatory basis with close monitoring of electrolyte response. Hospitalization is reserved for individuals who are symptomatic, require frequent electrolyte monitoring, or require IV supplementation. Aggressive repletion is necessary, as demonstrated in Figure 1. Individuals with electrolyte abnormalities usually require supplementation for the duration of parenteral therapy. While electrolyte disturbances do not require discontinuation of injectable therapy, capreomycin may be replaced by an aminoglycoside, if susceptibility to an alternative injectable is demonstrated.

The use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride) was not associated with resolution of hypokalemia in our cohort; however, we reserved amiloride for those individuals with refractory electrolyte disturbances and used lower doses compared with previously mentioned literature. Of note, caution should be used when potassium-sparing diuretics are administered in conjunction with potassium supplements, since hyperkalemia or orthostasis can result.

Despite an association between hypokalemia and mortality, rates of poor treatment outcome and mortality were not significantly greater among those patients with electrolyte disturbances. Nonetheless, among individuals with hypokalemia, failure to resolve this electrolyte disorder was significantly associated with death. Whether hypokalemia contributed to their mortality or reflects another factor associated with greater morbidity remains to be determined. Of note, the average duration from time to diagnosis of hypokalemia to death was 4.1 months among the eight individuals who had hypokalemia and died. Therefore, it is unlikely patients died too quickly for electrolyte disorders to be corrected. While no autopsies were performed, none of these deaths were believed to be due to cardiac arrhythmia, seizure, or coma. A larger cohort will be needed to understand the contribution of electrolyte disorders to the mortality of individuals treated for MDR-TB.

Our study does have certain limitations, including a limited sample size. We plan to assess a larger cohort in the future, with the hopes of understanding the risk factors associated with occurrence and persistence of electrolyte imbalances, as well as the relationship between electrolyte disorders and mortality. Furthermore, while this analysis has been helpful in shaping our management strategies in Peru, relevance to other settings may vary. Our
cohort is relatively young and healthy. Importantly, there were no patients with HIV within this cohort. Therefore, our management and treatment approach may be less relevant for programs with high rates of patients who are older or HIV positive.

Given the subtle symptoms and significant morbidity associated with electrolyte disturbance, close monitoring and aggressive management is mandatory. However, even in a resource-poor setting such as Lima, Peru, this serious adverse reaction can be successfully managed. In Lima, a key component in the management of all adverse effects associated with MDR-TB therapy has been the utilization of simple algorithms to guide surveillance and treatment strategies. Once such a protocol was implemented for the management of electrolyte disturbances, more complete screening and earlier diagnosis have been achieved.

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