Retrospective Analysis of a Novel Regimen for the Prevention of Venous Thromboembolism in Nephrotic Syndrome

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Abstract

Background and objectives Venous thromboembolism (VTE) occurs in 7%–40% of nephrotic patients. The risk of VTE depends on the severity and underlying cause of nephrotic syndrome. This study investigated the use of low-dose prophylactic anticoagulation to prevent VTE in patients with nephrotic syndrome caused by primary glomerulonephritis.

Design, setting, participants, & measurements Since 2006, all patients presenting with nephrotic syndrome to Imperial College Kidney and Transplant Centre have been considered for treatment with a novel anticoagulation prophylaxis regimen. All cases of nephrotic syndrome secondary to primary membranous nephropathy, minimal-change disease, and FSGS over a 5-year period were retrospectively reviewed. Patients with serum albumin <2.0 g/dl received prophylactic-dose low-molecular-weight heparin or low-dose warfarin; patients with albumin levels of 2.0–3.0 g/dl received aspirin, 75 mg once daily. All thrombotic events and bleeding complications were recorded.

Results A total of 143 patients received the prophylactic anticoagulation regimen. Median follow-up was 154 weeks (range, 30–298 weeks). The cohort had features associated with a high risk of developing VTE; 40% of the cohort had an underlying diagnosis of membranous nephropathy, and the initial median serum albumin was 1.5 g/dl (range, 0.5–2.9 g/dl). No VTE occurred in patients established on prophylaxis for at least 1 week. VTE was diagnosed in 2 of 143 patients (1.39%) within the first week after presentation and starting prophylaxis. In both cases, it is unclear whether the thrombus had developed before or after the start of prophylaxis. One of 143 patients (0.69%) received urgent blood transfusions and procedures to manage occult gastrointestinal bleeding. No other bleeding events occurred in patients receiving prophylaxis.

Conclusions This regimen of prophylactic antiplatelet or anticoagulant therapy appears effective in preventing VTE in nephrotic syndrome, with relatively few hemorrhagic complications.


Introduction

Venous thromboembolism (VTE) is a well-recognized complication of nephrotic syndrome that carries significant morbidity and mortality (1). Primary GN is the underlying pathology in approximately 82% of nondiabetic cases. Most of these are caused by membranous nephropathy (MN), minimal-change disease (MCD), or FSGS (2). The underlying cause of nephrotic syndrome influences thrombotic risk; MN is associated with the greatest risk (3), but significant risk is also associated with MCD and FSGS (4). The degree of hypoalbuminemia also influences risk, with more severe hypoalbuminemia correlating with increased thrombotic risk (5). This high rate of VTE contributes significantly to the morbidity and mortality seen in GN, with annual mortality rates of up to 10% for VTE in MN (1).

Despite the well-established risk of VTE in nephrotic syndrome, the most effective method of VTE prophylaxis is unclear (3,6). However, to prevent the significant morbidity and mortality associated with VTE, many nephrologists prescribe prophylactic anticoagulation in nephrotic syndrome.

The aim of this study was to investigate the risk and benefits of a low-dose prophylactic anticoagulation regimen to prevent VTE in patients with nephrotic syndrome secondary to MN, MCD, and FSGS. We present a retrospective analysis of an uncontrolled, nonrandomized application of a specific anticoagulant protocol over 5 years for the prevention of serious VTE in patients with primary nephrotic syndrome. To our knowledge, this is the first published clinical study of anticoagulation prophylaxis in nephrotic syndrome.
Materials and Methods

Since 2006, all adult patients presenting with nephrotic syndrome to Imperial College Kidney and Transplant Centre, London, have been considered for anticoagulation prophylaxis for the prevention of VTE. All patients presenting with nephrotic syndrome secondary to biopsy-proven primary MN, MCD, and FSGS from September 2006 to September 2011 were reviewed. Nephrotic syndrome was defined as an estimated daily level of proteinuria based on the urine protein-to-creatinine ratio of >250 mg/mmol on at least two separate occasions, in association with serum albumin <3.0 g/dl. Primary MN, MCD, and FSGS are the three most common glomerulonephritides causing nephrotic syndrome in these patients.

Investigations performed to exclude secondary causes of nephrotic syndrome included autoantibody screen, including serum antineutrophil antibodies, serum double-stranded DNA, complement C3 and C4 levels, and antineutrophil cytoplasmic antibodies; serum immunoglobulins and protein electrophoresis; random and fasting serum glucose levels; and serologic screening for hepatitis B and C virus. In addition, patients underwent renal ultrasonography before native renal biopsy. In view of the association of MN with malignancy, all patients with MN on biopsy were also screened for occult malignancy with computed tomography of the chest, abdomen, and pelvis.

The anticoagulation prophylaxis regimen for nephrotic syndrome was designed to stratify patients according to the severity of the nephrotic syndrome, as estimated by the serum albumin, because this is strongly associated with their risk of developing VTE. Patients presenting with or developing serum albumin levels <2.0 g/dl received low-molecular-weight heparin (LMWH) by subcutaneous injections (enoxaparin, 20 mg once daily or equivalent formulation). Each patient's albumin level was regularly reviewed in the clinic. Patients with hypoaalbuminemia <2.0 g/dl for >3 months were considered for a switch to low-dose warfarin, aiming for an international normalized ratio (INR) of 1.5–2.5. Patients in whom albumin level improved to 2.0–3.0 g/dl were switched to aspirin, 75 mg daily.

Patients who presented with, or progressed to, a serum albumin of 2.0–3.0 g/dl received daily aspirin, 75 mg. When the serum albumin was >3.0 g/dl, patients stopped the prophylaxis regimen. Patients therefore moved between treatment groups during follow-up according to their serum albumin; when patients had a serum albumin <2.0 g/dl, they received LMWH or warfarin; when patients had a serum albumin of 2.0–3.0 g/dl, they received aspirin; and when patients' albumin rose to >3.0 g/dl, the anticoagulation was stopped (Figure 1).

In addition to the prophylactic anticoagulation regimen, patients received treatment for their underlying glomerulopathy. This included optimizing blood pressure control, renin-angiotensin system blockade, and prescribing immunosuppressive therapy if indicated. Gastroprotection with a proton-pump inhibitor was routinely prescribed for all patients receiving corticosteroids.

Patients already taking anticoagulation therapy, including heparin, warfarin, or dual antiplatelet therapy, before presentation with nephrotic syndrome were excluded from the study. Patients who presented with an arterial or venous thrombotic event at the time of diagnosis of their nephrotic syndrome were also excluded and treated according to local guidelines. Patients with a history of VTE or pulmonary embolism were excluded if they were taking anticoagulation at the time of consideration for the study. Patients receiving single antiplatelet agents at presentation were included, and they continued the antiplatelet medication when the nephrotic syndrome had resolved. Clinical contraindications to prophylaxis were considered on a case-by-case basis. Patients presenting with ESRD were excluded from the study. They did not receive prophylaxis because of the confounding anticoagulant sequelae associated with uremia and because of the fact that they would receive heparin with hemodialysis.

Patient records were reviewed to record the number of VTE and bleeding events during the prophylactic VTE regimen. Thrombotic events included deep-vein thrombosis, pulmonary embolism, renal vein thrombosis (RVT), and arterial thrombosis. Patients were assessed for RVT at presentation with Doppler ultrasonography. This was repeated if an RVT was suspected on clinical grounds, for example, with deterioration in hypoalbuminemia or GFR. We did not screen patients for asymptomatic VTEs but investigated all patients who developed symptoms possibly attributable to VTE. All significant events suggesting possible bleeding were recorded, including hemorrhage requiring inpatient investigation, blood transfusions received, and investigations for anemia of unknown cause. Hemoglobin and albumin were monitored at each clinic visit throughout the study. The study adhered to the principles of the Declaration of Helsinki throughout the study period. The study was approved by the Imperial College Glomerulonephritis Research Group, our local institutional review board. Because we retrospectively reviewed anonymized data, we did not obtain consent from the participants.

Results

Over 5 years, 161 patients presented with nephrotic syndrome due to primary MN, MCD, or FSGS. Twelve (7.45%) presented with VTE at the time of diagnosis of their nephrotic syndrome and were excluded from the study. One patient was already taking dual antiplatelet therapy for ischemic heart disease and was also excluded. Two of the 161 patients were excluded from the prophylaxis regimen due to bleeding risk: one had chronic anemia and clinical evidence...
of gastrointestinal bleeding, and the other had chronic anemia and severe menorrhagia. Both were referred for further investigations. Three patients were lost to follow-up. Therefore, notes were reviewed for 143 patients receiving the regimen over 5 years (Figure 2).

Fifty-eight of 143 patients had an underlying diagnosis of MN (40.56%), 45 had MCD (31.37%), and 40 had FSGS (27.97%) (Table 1). The median age was 49 years (range, 20–85 years). The median serum creatinine at presentation was 0.94 mg/dl (range, 0.54–4.43 mg/dl). Ninety-one of 143 (63.64%) patients had severe nephrotic syndrome with a serum albumin, 2.0 g/dl (normal range, 3.2–5.5 g/dl) during their clinical follow-up. Of patients with a serum albumin, 2.0 g/dl, 31 of 91 (32.98%) had MN, 34 (37.35%) had MCD, and 26 (28.57%) had FSGS (Figure 3).

Median highest recorded urinary protein-to-creatinine ratio was 892 mg/mmol (range, 255–13000 mg/mmol). Duration of nephrotic syndrome in individual patients (Table 2), and, therefore, anticoagulation exposure, ranged widely.

Ninety-one of 143 patients (63.64%) received treatment with heparin at some point in the course of their disease. Because of a phobia of needles, one patient received warfarin instead of LMWH. Four patients were switched from LMWH to warfarin as a result of protracted hypoalbuminemia (serum albumin, 2.0 g/dl) at a median time of 20 weeks’ treatment (range, 13–29 weeks). The anticoagulant control achieved in these patients was good; 61% of INR recordings were in the 1.5–2.5 range and the highest recorded INR was 3.0.

Of 143 patients included, 51 (35.66%) received corticosteroid treatment for their nephrotic syndrome, either as sole therapy or in combination with other immunosuppressive agents. Sixty-six of 143 (46.15%) received immunosuppressive regimens that did not include corticosteroids; the regimens used included tacrolimus, mycophenolate mofetil, rituximab, and cyclophosphamide. Twenty-six patients (18.18%) received no immunosuppression. Eleven (18.97%) of the 58 patients with MN received corticosteroids, compared with 31 of 45 (68.89%) with MCD and 9 of 40 (22.50%) with FSGS.

During the 5 years of the study, no clinical VTE occurred in patients established on prophylaxis for at least 1 week. Two of the 143 patients (1.39%) were diagnosed with VTE during the first week from presentation and start of VTE prophylaxis. Specifically, pulmonary embolism occurred in one patient with MCD 6 days after starting the prophylaxis regimen and in one patient with MN 5 days after presenting, when his prophylaxis was stopped for 48 hours to facilitate a native renal biopsy. Both diagnoses were made with computed tomographic pulmonary angiography. In both cases, it was unclear whether the original thrombus had formed before or after the start of prophylaxis. Both these patients were successfully treated with full-dose LMWH, followed by warfarin.

No patients died during the study. One patient of 143 (0.69%) receiving prophylaxis was admitted urgently with gastrointestinal hemorrhage. This 77-year-old man with FSGS had a duodenal ulcer on upper gastrointestinal endoscopy and required inpatient blood transfusion for serum hemoglobin of 6.7 g/dl (normal range, 11.5–16.0 g/dl). His serum albumin was 2.8 g/dl at the time, and he was therefore receiving 75 mg aspirin daily. He had started a course of oral corticosteroids 6 days before presenting and was taking a proton-pump inhibitor. Two of 143 patients (1.40%) developed anemia and had elective blood transfusions and investigations to look for occult gastrointestinal bleeding. Both were male patients with MN; one was 70 years old with an ulcerated sigmoid polyp on colonoscopy, and a hemoglobin of 6.8 g/dl. His serum albumin was 2.2 g/dl at the time, and, hence, he was receiving aspirin. He was not taking a proton-pump inhibitor. The second patient was age 71 years and had multiple colonic adenomas on colonoscopy. His serum hemoglobin was 7.7 g/dl. He had a serum albumin of 1.8 g/dl and was receiving LMWH at the time of transfusion. Neither of these patients was receiving corticosteroids. No other patients had confirmed bleeding events. No other patients received blood transfusions for hemorrhage.

During the 5-year period, 4 additional patients (2.80%) underwent elective endoluminal gastrointestinal investigation:
glomerulopathy: MN, MCD, and FSGS.

Discussion

In both cases, gastritis with no signs of blood loss was the only abnormality identified. Neither was anemic. Both were taking aspirin as per the regimen, and both were taking a proton-pump inhibitor. In patients who underwent endoscopy for symptoms of dyspepsia, colonoscopy with no source of bleeding identified. Two patients underwent endoscopy for symptoms of dyspepsia. Neither was anemic. Both were taking aspirin as per the regimen, and both were taking a proton-pump inhibitor. In both cases, gastritis with no signs of blood loss was the only abnormality identified.

Two of these 4 patients had symptoms of lower gastrointestinal bleeding, although neither was anemic. One patient was taking LMWH and one aspirin. Both patients underwent colonoscopy with no source of bleeding identified. Two patients underwent endoscopy for symptoms of dyspepsia. Neither was anemic. Both were taking aspirin as per the regimen, and both were taking a proton-pump inhibitor. In both cases, gastritis with no signs of blood loss was the only abnormality identified.

Four patients developed malignant lesions. One patient developed lung cancer. His underlying diagnosis was MN. Two patients developed prostate cancer: the underlying diagnosis was MN in one patient and MCD in the other. One patient with MCD developed leukemia. None of these patients had VTE or bleeding events while receiving the prophylaxis regimen.

Table 1. Cohort characteristics at initiation of the prophylaxis regimen, both for the entire cohort and for each type of glomerulopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=143)</th>
<th>MN (n=58)</th>
<th>MCD (n=45)</th>
<th>FSGS (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) (yr)</td>
<td>48.7 (20.0–85.5)</td>
<td>54.3 (26.0–85.5)</td>
<td>48.7 (20.0–82.2)</td>
<td>48.1 (24.0–84.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76 (53.1)</td>
<td>35 (60.3)</td>
<td>23 (51.1)</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (46.9)</td>
<td>23 (29.7)</td>
<td>22 (48.9)</td>
<td>22 (55.0)</td>
</tr>
<tr>
<td>Median follow-up (range) (wk)</td>
<td>154 (30–298)</td>
<td>129 (44–298)</td>
<td>191 (930–285)</td>
<td>159 (30–279)</td>
</tr>
<tr>
<td>Median serum creatinine at presentation (range) (mg/dl)</td>
<td>0.94 (0.54–4.43)</td>
<td>0.89 (0.58–2.85)</td>
<td>0.90 (90.54–3.59)</td>
<td>1.52 (0.54–4.43)</td>
</tr>
</tbody>
</table>

MN, membranous nephropathy; MCD, minimal-change disease.

Because of the degree of hypoalbuminemia and predominance of MN, our cohort of patients was at relatively high risk of developing VTE. From a retrospective study of patients with MN, Lionaki et al. concluded that the severity of hypoalbuminemia is significantly associated with VTE risk; each 1.0-g/dl decrease in albumin level was associated with a 2.13-fold increased risk of VTE, and a serum albumin level <2.8 g/dl was the threshold associated with significant VTE risk (7). In our cohort, 98.60% (141 of 143) of patients had an albumin <2.8 g/dl, and the majority (64%) had a serum albumin level <2.0 g/dl. The duration of hypoalbuminemia in our cohort was also significant; the median times with serum albumin <2.0 g/dl and 2.0–3.0 g/dl were 6.4 weeks and 14.7 weeks. A large retrospective cohort study of >1300 patients with median follow-up time of 63 months found the number of patients with at least one VTE to be 31 of 395 (7.9%) for MN compared with 11 of 370 (3.0%) for FSGS, equating to a hazard risk for VTE of 10.8 for MN and 5.9 for FSGS compared with IgA nephropathy (8).

Although the rate of VTE has been documented as higher in the first 6 months from presentation (4,9), the risk of VTE is not isolated to the time of presentation (hence the need for thromboprophylaxis). Barbour et al. found a median time until development of VTE in patients with GN of 272 days, with only 70% VTE episodes occurring within the first 2 years (8). This finding suggests that without prophylaxis, our cohort would have had a comparatively high rate of VTE through the 5-year follow-up. The fact that no patients developed VTE after 1 week on the regimen suggests that our cohort had a significant reduction in symptomatic VTE events secondary to the anticoagulation prophylaxis they received.

Because there is no placebo group against which to compare our results, it is unfortunately impossible to calculate our cohort’s absolute rate of VTE without prophylaxis. This appears to be the first report of a prophylactic regimen to prevent VTE in nephrotic syndrome; thus, indirect comparison with other protocols is also difficult. Some studies have used mathematical analysis models to suggest a benefit for VTE prophylaxis in nephrotic syndrome secondary to MN. However, they did not document actual patient experience or outcomes and were limited to a single glomerular pathology (10,11). Comparison with other cohorts is also often limited by unclear treatment protocols. For example, although Barbour et al. documented a VTE rate of 7.85% in MN and 2.87% in

Figure 3. Numbers of patients with serum albumin <3.0 g/dl and <2.0 g/dl for the overall cohort and for each individual type of glomerulopathy: MN, MCD, and FSGS.

Two of these 4 patients had symptoms of lower gastrointestinal bleeding, although neither was anemic. One patient was taking LMWH and one aspirin. Both patients underwent colonoscopy with no source of bleeding identified. Two patients underwent endoscopy for symptoms of dyspepsia. Neither was anemic. Both were taking aspirin as per the regimen, and both were taking a proton-pump inhibitor. In both cases, gastritis with no signs of blood loss was the only abnormality identified.

Four patients developed malignant lesions. One patient developed lung cancer. His underlying diagnosis was MN. Two patients developed prostate cancer: the underlying diagnosis was MN in one patient and MCD in the other. One patient with MCD developed leukemia. None of these patients had VTE or bleeding events while receiving the prophylaxis regimen.

Discussion

The Imperial College regimen for the prevention of VTE in nephrotic syndrome appears to be effective and relatively safe in patients with primary MN, MCD, and FSGS. Over 5 years, no patients established on the regimen for >1 week developed VTE. The two patients who developed VTE did so after 5 and 6 days, and it was not clear whether the original thrombus had developed before or after presentation and initiation of the regimen. If the thrombus was already present in these cases, the regimen may have helped prevent the development of a larger thrombus with more serious sequelae.
Table 2. Serum albumin and proteinuria characteristics for the cohort receiving prophylaxis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest serum albumin (g/dl)</td>
<td>1.5 (0.5–2.9)</td>
</tr>
<tr>
<td>Highest urine protein-to-creatinine ratio (mg/mmol)</td>
<td>892 (255–13,000)</td>
</tr>
<tr>
<td>Duration of hypoalbuminemia &lt;2.0 g/dl (n=91) (wk)</td>
<td>6.4 (0.14–245)</td>
</tr>
<tr>
<td>Duration of hypoalbuminemia 2.0–3.0 g/dl (n=143) (wk)</td>
<td>14.7 (0.43–308.43)</td>
</tr>
</tbody>
</table>

Values are expressed as the median (range).

FSGS (8), information on the proportion of their patients receiving anticoagulation prophylaxis was not included. The rate of hemorrhagic complications with this regimen was low. Over 5 years, only 1 of 143 patients was admitted urgently with hemorrhage while receiving the regimen. On investigation for anemia, 2 additional patients were found to have evidence of occult bleeding. Although the number of patients was small, there was no obvious association of gastrointestinal bleeding with underlying glomerular pathology, aspirin or heparin prophylaxis, or the use of proton-pump inhibitors. The apparent safety of this regimen may have been influenced by the immunosuppressive agents used. Reflecting the local preference for steroid-sparing immunosuppression regimens for glomerular pathology (12), our cohort had a relatively low rate of corticosteroid use, with 35.66% of the entire cohort (22.92% of patients with MN, 68.89% of those with MCD, and 22.50% of those with FSGS) receiving steroids.

The regimen’s approach to anticoagulation choice and dosing may also be a factor in its apparent safety. Although there is a low threshold for providing prophylaxis, reflecting the need to address the significant risk of VTE in nephrotic syndrome, the regimen was designed to provide relatively cautious anticoagulation with prophylactic rather than treatment doses of LMWH and target INR levels of 1.5–2.5. The regimen is also tailored to reflect changes in serum albumin during the disease course. This allows aggressive prophylaxis, and the concurrent unavoidable risk of hemorrhage, to be selectively applied only when thrombotic risk is greatest. The centralized design of renal care at our center may also contribute to the regimen’s success; patients with primary glomerular disorders are closely followed-up by a small group of consultants at a single tertiary center, facilitating uniform adherence to management protocols.

The Imperial College anticoagulation regimen supports a role for aspirin in VTE prevention in nephrotic patients. Although heparin-based anticoagulants have a weight of evidence demonstrating their benefit in preventing VTE in postoperative and medical inpatients (12–14), they are also associated with higher bleeding complication rates than are antiplatelet medication (15). Traditionally, it was argued that antiplatelet agents were ineffective as VTE prophylaxis because of the prothrombotic milieu in veins featuring platelet-independent, low-flow fibrin aggregation. However, in nephrotic syndrome, it is possible platelets play a more pivotal role in thrombus formation, as suggested by increased markers of platelet activation (2), relative thrombocytosis, and increased relative levels of von Willebrand factor, free arachidonic acid, and thromboxane A2 (16). Aspirin use has been shown to have significant clinical benefits in preventing VTE in high-risk medical patients (17) and, recently, in preventing VTE recurrence after unprovoked primary VTE (18,19). Similar to patients with primary VTE, patients with sustained nephrosis have ongoing, ill-defined prothrombotic risk.

Our results highlight areas warranting further thought and investigation. The two VTE episodes we identified occurred in the first week from presentation. Perhaps anticoagulation should be more aggressive in this period, with shorter cessation of heparin for invasive procedures, such as biopsy, for example, by running unfractionated heparin infusions. The three patients with identified bleeding events were male and older than 70 years of age. A more cautious anticoagulation approach or prophylaxis screening for occult gastrointestinal lesions may be warranted in this group. Many newer anticoagulant agents are now in use, and trials to compare different antiplatelet and anticoagulation agents are needed (20). Given the success of the Imperial College regimen in patients with nephrotic syndrome, its application to nonproteinuric patients who have other ongoing prothrombotic risk factors, such as immobility or a history of unprovoked VTE, should be assessed.

The main limitations of this study are its retrospective design and lack of control group for comparison. Clearly, more research is required. It is also not possible to guarantee adherence of every patient to the protocol medication. Although a randomized study could be limited by the ethical difficulty of randomly assigning severely nephrotic patients to nonprophylaxis, an alternative control group could be patients with identical glomerular pathology but non-nephrotic proteinuria. This may also delineate whether the underlying pathology or the severity of nephrosis is the biggest contributor to thrombotic risk. Similarly, and considering the suggestion that thrombotic risk may be related to underlying diagnosis, studies of prophylaxis regimens based on a patient’s glomerular pathology are warranted. Prospective trials of prophylaxis in patients with less severe hypoalbuminemia where the thrombotic risk is less well defined, would also inform patient care. Finally, this study focused on just primary MN, MCD, and FSGS. This reflects an attempt to initially limit confounding factors, such as malignancy or lupus anticoagulants. The use of this regimen in nephrotic patients with other underlying causes requires further investigation.

In summary, this study demonstrates a prophylaxis regimen for the prevention of VTE in patients with nephrotic syndrome that is simple and appears to be effective and relatively safe. This was a retrospective review of a single center’s experience in a specific cohort of patients, and its limitations should be recognized. However, it is the first published clinical research available on the risks, benefits, and effectiveness of VTE prophylaxis in nephrotic syndrome. It provides valuable clinical information that can direct the management of an otherwise difficult complication associated with significant morbidity and mortality.
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Disclosures
None.

References

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