Approach to the Highly Sensitized Kidney Transplant Candidate

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Abstract

For patients with ESRD, kidney transplant offers significant survival and quality-of-life advantages compared with dialysis. But for patients seeking transplant who are highly sensitized, wait times have traditionally been long and options limited. The approach to the highly sensitized candidate for kidney transplant has changed substantially over time owing to new advances in desensitization, options for paired donor exchange (PDE), and changes to the deceased-donor allocation system. Initial evaluation should focus on determining living-donor availability because a compatible living donor is always the best option. However, for most highly sensitized candidates this scenario is unlikely. For candidates with an incompatible donor, PDE can improve the prospects of finding a compatible living donor but for many highly sensitized patients the probability of finding a match in the relatively small pools of donors in PDE programs is limited. Desensitization of a living donor/recipient pair with low levels of incompatibility is another reasonable approach. But for pairs with high levels of pathologic HLA antibodies, outcomes after desensitization for the patient and allograft are less optimal. Determining the degree of sensitization by calculated panel-reactive antibody (cPRA) is critical in counseling the highly sensitized patient on expected wait times to deceased-donor transplant. For candidates with a high likelihood of finding a compatible deceased donor in a reasonable time frame, waiting for a kidney is a good strategy. For the candidate without a living donor and with a low probability of finding a deceased-donor match, desensitization on the waiting list can be considered. The approach to the highly sensitized kidney transplant candidate must be individualized and requires careful discussion among the transplant center, patient, and referring nephrologist.


Case Presentation

A 38-year-old black man with type 2 diabetes and ESRD due to diabetic nephropathy presented for evaluation for a second kidney transplant. He was receiving hemodialysis for 1 year before undergoing his first deceased-donor kidney transplant in 1997. His immediate post-transplant course was uncomplicated, without known episodes of rejection. The graft began to fail about 4 years before his resumption of dialysis. A renal allograft biopsy at that time showed calcineurin inhibitor toxicity and chronic allograft nephropathy but no acute rejection. He resumed peritoneal dialysis in 2010, at which time his immunosuppression was weaned to low-dose prednisone, 5 mg daily. He is blood type A, which portends wait times of 3–4 years in our organ procurement organization (OPO), the geographically defined unit of organ allocation. An historical panel-reactive antibody (PRA) on full immunosuppression was 0% but repeat testing at current evaluation reveals a calculated panel-reactive antibody (cPRA) of 100% with multiple HLA antibodies against class II antigens. See candidate HLA typing in Table 1. His other medical problems include obesity (body mass index, 40 kg/m²), hypertension without significant end-organ damage, and diabetic neuropathy. He has no potential living donors. His physical examination was unremarkable. A right-lower-quadrant renal allograft was nontender. After completion of routine pretransplant evaluation, the candidate was placed on the active wait list for transplant. At the time of implementation of the new organ allocation system in December 2014, he had accrued 48 months of waiting time and had not received any organ offers.

HLA Testing in Kidney Transplantation

HLA molecules are highly polymorphic and vary considerably among individuals within a population. They are the principal mechanism by which the immune system identifies self from nonself and not only are critical in responding to commonly encountered foreign invaders, such as viruses and bacteria, but are the key instigator in the allograft rejection response. Exposure to nonself HLA antigens can lead to formation of anti-HLA antibodies, a process known as sensitization. This occurs primarily via three types of exposure (listed here by increasing sensitizing potential): blood transfusions, pregnancy, and solid organ transplant. Rare cases of sensitization can occur without these events and are thought to be due to crossreactive antigens from other exposures, such as viruses. Approximately 15% of wait-listed candidates have some degree of sensitization. High levels of sensitization are associated with longer wait times and increased likelihood of being removed from or dying while on the wait list (1).
For the sensitized renal transplant candidate, finding a donor for whom the candidate has no or very low levels of preformed HLA antibodies is the preferred approach and is associated with better allograft outcomes (2–5). The HLA antigen system is broken down into two broad categories based on their expression on cell membranes and their peptide configuration. Class I antigens (HLA-A, -B, and -C antigens) are expressed on the surface of all nucleated cells. Class II antigens (HLA-DR, -DQ, and -DP) are normally expressed only on antigen presenting cells, but under the influence of cytokines can be expressed on other epithelial and endothelial cells, and therefore can be the targets for immune-mediated injury. The genes for the class I and II HLA types are closely linked and found on the short arm of chromosome 6 in humans; although crossover between chromosomes can occur, most offspring inherit one haplotype of class I and II alleles from each parent (6,7).

The modalities available to characterize the recipient’s pretransplant immunologic risk and detect preformed HLA antibodies have evolved over time. In their seminal work in 1969, Patel and Terasaki described the first test to evaluate for the presence of preformed antibodies, known as the complement-dependent cytotoxicity (CDC) crossmatch (8). A positive CDC crossmatch very effectively predicted the risk of hyperacute rejection, and excluding recipient/donor pairs on the basis of this test dramatically reduced this dreaded complication. With the use of flow cytometry, in 1983 the flow cytometric crossmatch (FCXM) became available, increasing sensitivity for antibody detection (9). In the last 15 years, solid-phase assays, including the Luminex platform, have allowed the detection of specific HLA antibody types (10). If the specificity of the HLA antibody is against the donor, it is known as a donor-specific antibody (DSA). The basic techniques for detection of HLA antibodies are outlined in Table 3. Even in the setting of a negative crossmatch, presence of DSA is associated with decreased allograft survival (11–14). Research is ongoing to better define the risk of HLA antigens in solid organ transplant, including differences in risk by HLA IgG subtype and importance of complement binding with C4d (15,16).

The targets for antibodies directed against HLA molecule are known as epitopes. An epitope typically but not always consists of a three–amino acid sequence on the HLA molecule that is exposed on the exterior of the molecule (17).

Each HLA molecule has multiple antibody-binding sites, and different polymorphisms of the HLA molecule may share epitopes, permitting crossreactivity between HLA types. These shared epitopes between HLA molecules are the basis of the crossreactive groups, whereby development of antibodies against one HLA molecule can result in reactivity against multiple HLA types. This additive increase in presensitization can significantly hamper our ability find acceptable organ matches.

To better quantify the odds of finding an acceptable donor within the existing donor pool, the cPRA was developed (18). This differs from the traditional PRA testing in which candidate serum is tested against lymphocytes from randomly selected people from the population, and the result is expressed as a percentage of the randomly selected lymphocyte donors with reactivity. The advent of solid-phase assay testing now allows for the identification of the specific HLA antibodies produced by a candidate. Many centers use the Luminex platform, which allows for detection of antibody as a semi-quantitative measure reported as mean fluorescent intensity (MFI). Given the variability in the test results, this number provides a rough estimation of antibody levels, with lower MFI values indicating lower levels of circulating antibody and higher MFI values suggesting higher levels and increased risk of alloimmune response. HLA antibodies detected at a level anticipated to result in a high rate of rejection in the serum of candidates are designated as unacceptable. Through use of HLA frequency data from the donor population in the United States and the unacceptable HLA antigens for a potential candidate, the probability of finding a donor can be determined. The cPRA is the percentage of donors the candidate would likely react against and is expressed as a percentage. Thus, if the candidate cPRA is 75%, the expected odds that a donor would be crossmatch negative is 25%.

Criteria for determining unacceptable HLA antigens vary widely by center and have major implications for finding acceptable donor matches. The sweet spot for designating unacceptable antigens is to set the levels just low enough to avoid positive crossmatches but high enough to allow the candidate to receive as many organ offers as possible. At our center, we designate unacceptable antigens at MFI values exceeding 4000. These unacceptable antigens are listed in the United Network for Organ Sharing (UNOS) databases; recipients will not be eligible for donors with these HLA types and will be automatically excluded from match runs. This allows for a "virtual crossmatch" to predict crossmatch results during organ allocation. Implementation of the cPRA has improved efficiency of organ allocation by decreasing the number of positive crossmatches, which must still be performed before transplantation, and late organ declines (19,20). The unacceptable antigens for our renal transplant candidate are shown in Table 2.

### Table 2. HLA typing for renal transplant candidate

<table>
<thead>
<tr>
<th>Candidate HLA Typing</th>
<th>Class I—A: 23</th>
<th>A: 30</th>
<th>B: 18</th>
<th>B: 42</th>
<th>CW: 5</th>
<th>CW: 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II—DR: 18</td>
<td>DR: 14</td>
<td>DQ: 4</td>
<td>DQ: 5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Unacceptable antigens for renal transplant candidate

| DR: | 1 4 7 8 11 12 13 15 16 103 |
|     | DR51 \(52\) \(53\): 51 |
| DQ: | 2 6 7 8 9 |

An HLA antigen is designated as unacceptable at our center if the mean fluorescent intensity exceeds 4000.
Evolving Approach to the Highly Sensitized Candidate

A primary goal in transplant is to find donor/recipient pairs with the least amount of incompatibility. The options available to the sensitized candidate are greater if he or she has a living donor, even if the donor is incompatible. In the highly sensitized recipient, an organ with a negative crossmatch may not be easily attainable and desensitization to lower the levels of preformed antibodies to prevent early, hyperacute, and accelerated acute rejection may be the only feasible option for transplant. While hyperacute rejection is rare in the desensitized candidate, the rates of acute antibody-mediated rejection (AMR) and allograft loss are higher (21). Despite the less than ideal allograft outcomes in desensitized recipients, they have a survival advantage with transplant compared with dialysis in most cases (22). Figure 1 outlines the basic approach to the highly sensitized candidate for renal transplant.

Candidates with mild to moderate levels of sensitization can expect only modest increases in wait times to deceased-donor transplant. The theoretical number of potential donor offers needed to have a high probability of an acceptable match can be determined using the following equation:

\[
\text{Probability of finding an acceptable match} = 1 - (cPRA)^n
\]

where \(n\) = number of potential donors (23).

Table 3. Techniques for detection of HLA antibodies

<table>
<thead>
<tr>
<th>Technology</th>
<th>Testing</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Sensitivity(^a)</th>
<th>Specificity(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement-dependent cytoxic crossmatch</td>
<td>Donor lymphocytes are incubated with candidate serum and complement added. A vital dye is used to assess for cell lysis (\text{via}) activation of the complement system. Cell death is interpreted as a positive result.</td>
<td>Highly predictive for hyperacute rejection.</td>
<td>Visual assessment of results can be subjective. Cannot detect noncomplement binding or low-level antibodies.</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Flow cytometric crossmatch</td>
<td>Donor lymphocytes are exposed to candidate serum and incubated with fluorescent-labeled antibodies for human T and B cell subsets. Lymphocytes analyzed using flow cytometry to evaluate for IgG antibody binding. A positive result is reported as mean channel shift.</td>
<td>Semiquantitative. Increased sensitivity to low-level antibody. Allows for independent analysis of effect on T and B lymphocytes. Rapid results possible.</td>
<td>Higher sensitivity of testing may lead to false-positive results.</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Solid-phase assays: bead based (e.g., Luminex)</td>
<td>Purified HLA molecules immobilized onto solid surface.</td>
<td>Can detect specific antigens a candidate has antibodies against.</td>
<td>Lack of standardization and antigen variability. Interference by external factors (IVIG, antithymocyte globulin) and intrinsic factors (e.g., autoantibody, immune complexes, high levels of IgM). Significant interlaboratory variability. Unclear what constitutes a significant result.</td>
<td>++++</td>
<td>+</td>
</tr>
</tbody>
</table>

\(+, +++, +++, and ++++\) indicate increasing levels of sensitivity and specificity. IVIG, intravenous immunoglobulin.

\(^a\)Sensitivity for detection of donor-specific antibody.

\(^b\)Specificity for clinically significant antibody mediated rejection.
For a candidate with a cPRA of 95%, the number of donors needed in order to have a 95% chance of finding an acceptable match is about 60. For lower cPRA values, that number is considerably less. For a blood type O candidate with a cPRA of 95% who has attained enough wait time to be near the top of the transplant list in an average-sized OPO with 60 blood type O donors a year, the candidate could reasonably be expected to receive an organ within one year. Because blood types are not distributed equally among the population, recipients with less frequently occurring blood types can expect longer waits. Current blood type distribution among donors is blood type O, 46%; A, 38%; B, 12% and AB, 4%. The current allocation system allows AB candidates to share blood type A donor organs, effectively making blood type B the most disadvantaged candidate group in terms of donor pool size. For candidates with cPRAs >95% and especially those that approach a cPRA of 100%, the number of donors needed in order to have a high probability of finding an acceptable match increases exponentially. For instance, to achieve a 95% probability of finding an acceptable donor, a candidate with a cPRA of 99% would need to be part of 300 potential donor match runs, while a candidate with a cPRA of 99.5%, 99.9%, or 99.99% would need to be part of 600, 3000, and 30,000 match runs, respectively (Table 4). For purposes of listing and allocation, the cPRA is considered as a rounded integer value. Within the 100% cPRA designation, the probability of a match varies enormously according to the unrounded value. Approximately 13% of the 100% cPRA listed candidates have an unrounded cPRA ≥99.99%. For these candidates, waiting on the list for an acceptable match may be futile.
Among sensitized candidates, distribution of cPRA values is not uniform (Figure 2). Sensitized candidates with cPRA >95% make up approximately 20% of the sensitized candidates and peaks at 100% cPRA. This occurs for two reasons. First, highly sensitized candidates are less likely to find donors and accumulate on the list, while less sensitized individuals are more efficiently transplanted and removed from the candidate pool. Second, as stated earlier, there are many shared epitopes between HLA types, and sensitization due to exposure to one HLA type can result in sensitivity to multiple HLA types, leading to high levels of sensitization. For the purposes of this discussion, highly sensitized candidates are defined as those with a cPRA >95%.

To improve transplant rates among highly sensitized patients, the Organ Procurement and Transplantation Network (OPTN) implemented key changes to the kidney allocation system in December 2014 (24). Efforts were made to increase the pool of potential donors and improve chances of organ offers. First, a new sliding-scale point system was implemented, which awards points based on the cPRA level (Figure 3) (25). The additional points awarded for sensitization begins at a cPRA of 20% and increases exponentially as the cPRA approaches 100%, ensuring that the very highly sensitized contend for offers as soon as they are listed. The previous system only awarded four points to anyone with a cPRA≥80%. Second, efforts were made to expand the pool of available donors. While most organs are shared on a local level by OPOs, candidates with a cPRA of 99% have been offered priority access to donors at a regional level, generally increasing pool size by a factor of five, and candidates with a cPRA of 100% have priority access to donors at a national level, increasing the pool size by a factor of 50. Before the implementation of this policy, only about 2.5% of deceased-donor transplants went to patients with a cPRA≥98%. With the policy change, the rate has increased to >13% of deceased-donor transplants, demonstrating the benefit of these changes in allocation policy for these traditionally hard-to-transplant patients (26).

### Advances in Desensitization of the Highly Sensitized Candidate

Another tactic to improve the probability of transplant in the highly sensitized is to desensitize candidates waiting...
for an acceptable match on the deceased-donor waiting list. Pioneered by Dr. Stanley Jordan, protocols generally use infusions of intravenous immunoglobulin (IVIG) and rituximab to lower the titers of HLA antibodies in the candidate. After desensitization, the HLA antibody levels are rechecked using solid-phase antibody testing and the designation of the unacceptable antigens is modified according to the changes in HLA antibody levels. Lowering the number of unacceptable antigens decreases the cPRA and improves the chances of finding an acceptable donor. Desensitization on the wait list is labor intensive and costly, requires careful serologic monitoring, and necessitates exception to allocation rules from the OPTN. While some studies of this approach have shown improved transplant rates in highly sensitized candidates with acceptable post-transplant outcomes, albeit with a significant rate of early AMR (27,28), other studies have not replicated these results in highly sensitized candidates with cPRA levels >85%–90% (29–31).

The cost-effectiveness of this therapy must be balanced against the savings and health benefits associated with a successful kidney transplant compared with dialysis (32). Because this is not a use for these agents that is approved by the US Food and Drug Administration, payors may be reluctant to reimburse for treatments, so considerable effort is required to ensure that candidates are not burdened with unmanageable bills. Finally, and perhaps most important, the high cost of desensitization and tendency for antibody rebound after treatment requires that the candidates be near the top of the waiting list so as to contend for donor offers soon after treatment. For candidates who already have large amounts of waiting time, this is not an impediment. But for candidates who have not accumulated substantial time on the list, and whose high position on the waiting list is due to additional points given for sensitization, changing the unacceptable antigens in order to improve their chances of an offer also reduces their allocation points for sensitization; potentially moving them down the list and leading to loss of regional or national sharing priority. To overcome this issue, the OPTN has recommended that a variance from the allocation rules be obtained by the transplant center, which allows these candidates to keep the allocation points associated with their original, higher cPRA. The significant effort and resources needed to successfully implement this approach have limited its practice to only a few programs across the country.

Highly sensitized candidates with living donors have additional options for transplant with desensitization or paired donor exchange. If a candidate has an incompatible living donor, the recipient can be desensitized to allow direct donation or the pair can be enrolled in several national organizations (Alliance for Paired Donation, National Kidney Registry, or UNOS Kidney Paired Donation Program) that facilitate exchanges. As seen with recipients on the deceased-donor waiting list, the recipient’s unacceptable HLA antigens are identified and used to find donors in the paired exchange pool that have more favorable crossmatch results. The hope is to find a donor with both a negative CDC and FCXM; however, for the very highly sensitized this may be very difficult given the large pool size needed to find an acceptable match. For these candidates, considering ABO incompatible donor pairs will increase the pool size because the ABO barrier is much easier to overcome than HLA incompatibility. Alternatively, one could seek a donor/recipient pair

Figure 3. | Allocation points by calculated panel-reactive antibody (cPRA) in the old versus new kidney allocation system. Candidates listed for kidney transplant receive one point for each year on the list. Under the old kidney allocation system, candidates with cPRA scores >80% received four additional allocation points. Under the new allocation system, additional points are awarded for sensitization on a sliding scale. Candidates with cPRA scores of 98%, 99%, and 100% receive 24.4, 50.1, and 202.1 points respectively.
within the exchange with more favorable crossmatch results and pursue desensitization (33). Data from multiple transplant centers engaged in desensitization of recipients with living donors in the United States showed that the poorest outcomes among living donor/recipient pairs is between pairs with a positive CDC crossmatch before desensitization. Those with a negative CDC crossmatch and just a positive FCXM, or with just a DSA by Luminex without a positive CDC or FCXM do much better (Figure 4) (14). Therefore, the crossmatch results and DSA determination are useful risk stratification tools of the donor/recipient pairs with regard to allograft outcomes. Given the limited pool size of the exchange programs, for the highly sensitized it is often necessary to consider incompatible donors within the exchange, where it is felt the incompatibility is amenable to desensitization.

Desensitization involves the use of treatment regimens that decrease the preformed antibody levels directed toward the potential donor. Typically, the goal of therapy is to reduce the antibody level so the FCXM is negative or lower than a predetermined cutoff. Many different protocols have been used with varying success; however, most combine plasmapheresis, IVIG, rituximab, bortezomib, and early initiation of maintenance immunosuppression several weeks before the transplant (21,34–37). Single-center case series using these approaches for transplant have shown that 25%–50% of transplants will have an early AMR (28,36,38–40). Most of these rejections can be successfully treated, but a high rate of transplant glomerulopathy and chronic AMR leading to accelerated allograft failure is common (41). Even with prolonged post-transplant blockage of the complement system with eculizumab, which is more effective at preventing acute AMR, chronic damage to the allograft occurs, presumably by complement-independent pathways (35,42). Thus, the optimal desensitization protocol before transplant and the best maintenance immunosuppression program afterward remains to be determined and persistence of low-level DSA appears to have deleterious long-term effects on the graft. The advantage of the desensitization approach (as opposed to simply waiting for a better match on the waiting list) is the possibility of expedited transplant without a prolonged wait on dialysis. The disadvantages, however, are many, including higher cost, increased risk of infections and complications related to the higher intensity of immunosuppression, and known inferior outcomes for both the patient and the transplanted organ. But for some patients, this may be their only option.

Case Discussion
This patient illustrates some of the issues confronted when attempting to transplant the highly sensitized candidate. The first issue concerns continuation of immunosuppression after a failed kidney transplant. This patient did not have an elevated PRA while receiving his maintenance immunosuppression but developed a high PRA after his immunosuppression was lowered. Weaning immunosuppression increases sensitization in many candidates (43,44), and the decision of whether to maintain a low dose of immunosuppression depends on the anticipated wait time to the next transplant, whether from a living or deceased donor. If the candidate has a living donor or the projected wait for a deceased donor is short so the candidate can be transplanted
quickly, maintaining some immunosuppression to avoid sensitization should be considered. For candidates without a living donor who are projected to wait years for a transplant, the risks of infection due to continued immunosuppression while on dialysis may outweigh the potential benefit of preventing sensitization (45). In our particular candidate, the decision was made to wean his immunosuppression because of the expected long wait to deceased-donor transplant in the absence of a known living donor.

The implementation of the new kidney allocation system has revolutionized the way in which we manage the highly sensitized candidate. While our patient’s cPRA is listed as 100%, it was in reality 99.65%. To have a 95% chance of finding an acceptable match would require about 850 donor match runs. Approximately 11,500 deceased-donor kidneys are procured and transplanted from 6000 donors in a given year in the United States. With the significant advantage gained under the new allocation system, waiting on the list for a deceased donor was a good option for him. Desensitization, with its additional costs and complications, was avoided as a result of the benefits of the national priority and sharing given to highly sensitized candidates.

After implementation of the new allocation system in December 2014, the patient received a deceased-donor kidney transplant within 2 months (1 A, 1 B, and 1 DR mismatch). The B and T cell FCXM were negative before transplant. The patient received induction immunotherapy with methylprednisolone and thymoglobulin, 6 mg/kg. The patient did not receive a transplant within 2 months (1 A, 1 B, and 1 DR mismatch).

Questions

Dr. Mitchell Rosner (chair of medicine): How might you have approached your case study patient if his cPRA had been much higher, such as one of your listed patients with a cPRA >99.99% that you mention?

Dr. Keith: The approach to our patient should he have had a cPRA of 99.999% would have been quite different. Even with the additional 202 allocation points and national sharing for kidneys, meaning that he would have first priority for any organ that became available in the United States, his anticipated likelihood of receiving a deceased donor organ over the next 10 years is <25%. In this case, desensitization on the wait list would need to be considered.

Dr. Brendan Bowman (assistant professor of medicine): You mention that blood type and its frequency in the population can influence the options for your highly sensitized patients. How does this affect your patients with blood types B and AB, which are much less common than types O and A?

Dr. Keith: The new kidney allocation system has markedly changed the prospects for transplant of our patients who do not have living donors. But it remains a numbers game. Blood type AB candidates are given access to the blood type A donor pool so they are not disadvantaged by their relative infrequency in the population. For blood type B candidates, the situation is much different. The number of donors a potential candidate could have access to in a given time period depends on the OPO size and blood type frequency. The average OPO procures about 100–110 donors per year, but this number varies considerably, ranging from 23 to 323 in 2012. In our OPO, we have 12–15 blood type B donors annually. For a blood type B candidate with a cPRA of 98%, the number of donors needed to have a 95% chance of finding a suitable match is about 150. Thus, it may take many years to get this person transplanted from the wait list, despite a sizeable allocation of points for sensitization. For smaller OPOs, the expected wait would be even longer. If the candidate’s cPRA was 99% or 100%, they would have access to regional and national priority sharing, respectively, so that would increase their access to donors and considerably improve their transplant prospects. So approaches to the highly sensitized candidate should be tailored not just to their degree of sensitization but to their expected pool of available donors, taking into account their blood type, OPO size, and whether they qualify for regional or national sharing. For those candidates who have long-anticipated waits, revisiting efforts to find living donors, multiply listing with transplant centers in different OPOs, or desensitization on the wait list should be considered.

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This study used data from the SRTR. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

Disclosures
None.

References

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