American Society of Nephrology Quiz and Questionnaire 2012: Transplantation

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Summary
Presentation of the Nephrology Quiz and Questionnaire has become an annual tradition at the meetings of the American Society of Nephrology. It is a very popular session, as judged by consistently large attendance. Members of the audience test their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. They can also compare their answers in real time, using audience response devices, to those of program directors of nephrology training programs in the United States, acquired through an Internet-based questionnaire. Topics presented here include fluid and electrolyte disorders, transplantation, and ESRD and dialysis. Cases representing each of these categories, along with single-best-answer questions, were prepared by a panel of experts (Drs. Palmer, Fervenza, Brennan, and Mehrotra, respectively). The correct and incorrect answers were briefly discussed after the audience responses, and the results of the questionnaire were displayed. This article recapitulates the session and reproduces its educational value for a larger audience—that of the readers of the Clinical Journal of the American Society of Nephrology. Have fun.


Transplantation Case 1
A 51-year-old man with ESRD from IgA nephropathy received a one-haplotype matched living-related transplant from his brother. The baseline panel-reactive antibody level was 0%, and both donor and recipient were cytomegalovirus (CMV) seropositive. Induction immunosuppression included 1 mg/kg rabbit antithymocyte globulin (r-ATG) initiated intraoperatively, 2 mg/kg r-ATG given postoperatively on days 1 and 2, and 500 mg methylprednisolone. The recipient’s maintenance immunosuppression consists of tacrolimus (trough, 7 ng/dl); enteric mycophenolic acid salt, 360 mg twice daily; and prednisone, 5 mg daily.

He presents 25 days after transplantation with acute onset of fever, jaw pain, and bilateral hip and shoulder pain. He is receiving prophylactic trimethoprim-sulfamethoxazole, 400/800 mg/d, and valganciclovir, 450 mg/d. He also takes clopidogrel for a history of drug-eluting stent placement. He had a history of raising, hunting, and ingesting rabbits.

The physical examination findings include a body temperature of 36.5°C, BP of 134/84 mmHg, no graft tenderness, and pain and limited range of motion of the affected joints. The patient has a functioning left Cimino-Brescia fistula. His baseline serum creatinine level is 1.5 mg/dl, with an estimated GFR of 58 ml/min per 1.73 m². Laboratory data show a white blood cell count of 19,500 cells/mm³. The current serum creatinine level is 1.73 mg/dl. A urinalysis shows no protein or hematuria.

Question 1a (see Figure 1 for Responses of Program Directors and Attendees)
Which ONE of the following is the MOST likely diagnosis?
A. Antibody-mediated rejection
B. Recurrent IgA nephropathy
C. Serum sickness
D. Pneumocystis jiroveci infection
E. CMV infection

Discussion of Question 1a
The correct answer is C.

Although antibody-mediated rejection can occur in the absence of graft dysfunction, it is unlikely unless the transplant is high risk. It is usually diagnosed by surveillance biopsy (1). This transplant was a one-haplotype living-related organ in an unsensitized patient. In addition, the patient received r-ATG induction, which would further reduce the risk of early rejection even in living-donor recipients (2,3).

Whether recurrent IgA is more common after living-related transplants is controversial (4), but it would not be associated with the presenting symptoms. Use of r-ATG induction (5,6) and steroids reduce the risk of recurrence (7).

Serum sickness is the most likely cause, even though this is the patient’s first exposure to r-ATG. In one study of transplant recipients, almost 50% of patients had an exposure to rabbits before receiving thymocyte globulin. However, even in this group, serum sickness was relatively uncommon (8). Because serum sickness is uncommon, even in patients with a history of exposure to rabbits, such a history should not preclude the use of r-ATG in appropriate patients. This patient’s prior exposure to rabbits makes him statistically more likely to get serum sickness after his initial exposure to r-ATG. Pneumocystis jiroveci, formerly called Pneumocystis carinii, pneumonia does...
not usually present early, and prophylactic trimethoprim-
sulfamethoxazole nearly eliminates the risk of this condition
(9). Although the white blood cell count is elevated, this
most likely reflects reactive leukocytosis related to recovery
of the bone marrow after transplantation and resolution of
uremia.
CMV reactivation is rare with adequate prophylaxis,
making CMV infection unlikely (10). CMV also rarely re-
activates sooner than a month after transplantation, even
without prophylaxis (10,11). The elevated white blood cell
count would also be unusual because leukopenia with
monocytosis is more characteristic of CMV infection.

**Question 1b (See Figure 2)**
Which ONE of the following would be the MOST expedient treatment?

A. Plasmapheresis, intravenous immunoglobulin, and rit-
uximab initiated immediately
B. Plasmapheresis until symptom resolution
C. High-dose intravenous trimethoprim-sulfamethoxazole
D. Conversion valganciclovir to intravenous ganciclovir
E. Oral glucocorticoid burst and taper

**Discussion of Question 1b**
The correct answer is B.
It is highly likely that the patient has serum sickness, and
this question deals with its management. The possible
treatments for serum sickness include plasmapheresis and
glucocorticoid therapy.
The patient has a functional fistula, which can be used for
pheresis by a physician trained in extracorporeal therapies,
such as a nephrologist. Pheresis also serves as a diagnostic
and therapeutic option. Even a single plasmapheresis
session can markedly improve arthralgias (8). Glucocorti-
coids are an effective treatment for serum sickness, but
they take longer to work than pheresis. They may be prefer-
able if pheresis cannot be performed using the arterio-
venous fistula and it is necessary to place a central line for
pheresis, with its attendant risks of pneumothorax, bleed-
ing, or infection. If steroids are used, however, intravenous
administration may be preferred to oral.

**Transplantation Case 2**
A 64-year-old man had a previous transplant in 1998 that
had failed in 2003 secondary to recurrent membranous
glomerulopathy. He underwent a second transplantation
from a living-unrelated donor, with thymocyte globulin
induction in 2004. The HLA match was 2A, 2B, 1DR
mismatch, the donor was CMV seropositive, and the
recipient was CMV seronegative (D+/R–). The patient’s
maintenance immunosuppression regimen consisted of
tacrolimus (trough levels, 3–4 ng/ml); azathioprine, 150
mg/d; and prednisone, 5 mg/d. His baseline creatinine
level was 1.2–1.5 mg/dl. Eighteen months after transplan-
tation, an allograft biopsy is performed for persistent pro-
teinuria of 1.5 g/d. Pathologic examination reveals
membranous glomerulopathy with minimal signs of allo-
graff rejection. Serum creatinine level is 1.3 mg/dl, total
cholesterol is 154 mg/dl, triglycerides are 226 mg/dl, and
albumin is 3.9 mg/dl. No anti-HLA antibodies are detect-
able by single-bead assay. He has no edema.

**Question 2a (See Figure 3)**
Which ONE of the FOLLOWING would be the LEAST beneficial initial treatment?

A. Performing plasmapheresis until the results of an anti-
phospholipase A2 receptor (PLA2R) antibody level are
received
B. Alternating intravenous alkylating agents and high-dose
steroids in place of the azathioprine and low-dose steroids
C. Starting angiotensin-converting enzyme inhibitor
D. Augmenting tacrolimus dosage
E. Starting rituximab

**Discussion of Question 2a**
The correct answer is A.
The recognition that an antibody to PLA2R is associated
with membranous nephropathy in up to 75% of idiopathic
and recurrent membranous cases is one of the most
significant findings in nephrology in recent years (12–15).
However, the test is not routinely available, and there is
insufficient evidence that the result can be used as a sur-
rrogate marker of disease activity. In addition, up to 50% of
patients may not have an identifiable antibody and may still respond to therapy or remit spontaneously. Theoretically, plasmapheresis would remove antibody, but it would not stop antibody production. For this reason, A is the correct answer; all other options have some potential in the management of this patient.

This is a case of recurrent membranous in a patient who is already receiving a second-line agent and who lost a kidney from recurrent membranous. Although the patient is not overtly nephrotic, treatment seems indicated. According to Kidney Disease Improving Global Outcomes guidelines for the treatment of idiopathic membranous glomerulopathy, use of an alkylating agent alternating with high-dose steroids (the Ponticelli or modified Ponticelli regimen) is considered as first-line treatment, with cyclosporine or tacrolimus as second-line agents (16). There are no guidelines for treatment of the scenario of the case-patient.

Steroids remain one of the most potent anti-B cell and anti-plasma cell agents available in the immunosuppressive regimen. This provides the theoretical rationale for this approach. Prolonged high-dose steroids are associated with successful treatment, but high-dose steroids are not benign.

Use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and statin therapy is usually benign and an essential component of efforts to control the nephrotic syndrome; this is true even in a patient with a solitary kidney, such as a transplant recipient who probably has some degree of transplant renal artery stenosis.

Tacrolimus has been used for treatment of idiopathic membranous nephropathy in doses similar to what the patient is already receiving (17). Use of tacrolimus to treat recurrent membranous nephropathy is less well defined. In the face of recurrent skin cancers, augmentation of tacrolimus would not be the best option for this patient (see below), but plasmapheresis would still be the least reasonable option.

Rituximab has recently been demonstrated to be an effective treatment for de novo membranous nephropathy and recurrent membranous nephropathy (18–24). New evidence suggests that rituximab may be considered as first-line treatment for idiopathic and perhaps recurrent membranous nephropathy (25).

Further Case Description for Transplantation Case 2

The dose and frequency of rituximab administration have been based on those used for hematologic malignancies. Alternative dosing may be as effective, less inconvenience, and less costly (see below).

A single dose of rituximab, 500 mg (240 mg/m²), is administered. The daily protein excretion decreases to 130 mg, 8 months after infusion. Two years after rituximab infusion, the proteinuria increases to a peak of 1800 mg/d, and findings on renal biopsy are again consistent with recurrent membranous nephropathy. A second infusion of rituximab,
500 mg (240 mg/m²), leads to another remission, with daily protein excretion decreasing to 100 mg 3 months after infusion. Twenty-four months later, the patient again develops proteinuria of 1800 mg/d, and a repeat biopsy shows recurrent membranous glomerulopathy. The patient receives a third dose of rituximab, 500 mg (240 mg/m²), with resolution of proteinuria to 100 mg/d within 1 month of treatment. Five and a half years after transplant, approximately 30 months after the last rituximab dose, metastatic squamous cell carcinoma of the head and neck is diagnosed and the patient undergoes successful resection. Proteinuria increases to 1 g/d 2 years after the third infusion of rituximab (Figure 4). The patient states that he would rather die than return to dialysis.

**Question 2b (See Figure 5)**
Which ONE of the following is the MOST reasonable initial approach?

A. Discontinue tacrolimus  
B. Discontinue azathioprine  
C. Discontinue steroids  
D. Re-treat with rituximab  
E. Change azathioprine to rapamycin

**Discussion of Question 2b**
The correct answer is B.
The patient’s membranous nephropathy may be triggered by his skin cancers, and calcineurin inhibitors dramatically increase the risk for skin cancer. Tacrolimus is one of the most important immunosuppressive agents, and complete withdrawal would risk losing the graft. Reduction could be considered carefully because the patient has already stated that he would rather die than return to dialysis.

Although most transplant physicians probably think that azathioprine is one of the drugs most likely to cause skin cancer, a recent study showed that calcineurin inhibition results in a 200-fold increased skin cancer risk compared with the normal population and that the skin cancer risk with azathioprine is 3-fold less than that with calcineurin inhibitors; mammalian target of rapamycin inhibitors are associated with even lower rates of skin cancer (26). Because the patient would rather die than go on dialysis, reduction of azathioprine is probably the most reasonable initial approach. If the patient does not respond, re-treatment with rituximab should be considered because the patient lost his first allograft from recurrent membranous nephropathy and does not want to undergo dialysis.

**Figure 5.** | Answers for case 2, question 2b. Which ONE of the following is MOST reasonable initial approach? Correct answer B.

![Figure 5](image1.png)

**Figure 6.** | Dose effect of rituximab on CD20 cells. Even very-low-dose rituximab (50–150 mg/m²) depletes CD20 cells for at least 6 months and is similar to a more standard dose of 350 mg/m². Frequent dosing may not be necessary, and less frequent dosing could reduce costs and infectious risks. Modified from reference 30, with permission.

![Figure 6](image2.png)
Skin cancers are associated with human papillomavirus infection, and a reduction of steroids may allow for reduced warts and skin cancer. Complete discontinuation of steroids, especially late after kidney transplantation, is associated with deterioration of graft function and loss and would not be a good initial option (27).

This patient received relatively low-dose rituximab twice during a 4-year period. Rituximab is approved for treatment of chronic lymphocytic leukemia, non-Hodgkin B cell lymphoma, rheumatoid arthritis, Wegener granulomatosis, and microscopic polyangiitis. The approved dose is 375–500 mg/m² every 2–4 weeks according to the disease state, but the frequency of dosing outside of the U.S. Food and Drug Administration indications is unknown. Although the reports for treatment have used 375 mg/m² with repeat dosing, this large dose and frequency may be unnecessary. The CD20 lymphocyte peripheral and splenic depletion is profound and prolonged at doses as low as 50 mg/kg (Figures 6 and 7) (28–30). An abstract at the American Society of Transplantation 2012 annual meeting reported that doses of an average of approximately 100 mg/m² (or 200 mg per person), as was used in this case, were associated with long-term remission (31). There is an association between cancer and treatment of membranous nephropathy, as well as development of progressive multifocal leukoencephalopathy and post-transplant lymphoproliferative disorder, with repeated rituximab dosing. The patient is not overtly nephrotic, so repeat rituximab dosing would not be the best option.

Changing azathioprine to rapamycin may ameliorate the skin cancers (32). However, there is a significant risk of worsening proteinuria and inducing graft dysfunction, especially in this patient with proteinuria and recurrent membranous. A conversion would have to be done with close monitoring of urine protein excretion rates, renal function, and clinical adverse effects. A recent study showed that conversion to rapamycin significantly decreased the number of skin cancers but was associated with the development of adverse effects in ≥60% of the patients who converted (33).

Disclosures
None.

References


Published online ahead of print. Publication date available at www.jasn.org.