برخورد بالینی در بیمار با افزایش کراتینین بعد از پیوند کلیه

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INTRODUCTION

- Continued improvements in graft survival have led to widespread acceptance of renal transplantation as the preferred treatment for the majority of patients with end-stage renal disease.
- One of the most common complications of kidney transplantation is allograft dysfunction, which in some cases leads to graft loss.

INTRODUCTION

- Persistent dysfunction without timely intervention may lead to irreversible loss of allograft function and, eventually, allograft failure.
- The causes of kidney allograft dysfunction vary with the time (usually classified as immediate, early, and late period) after transplantation.

Table 1. Causes of true renal graft rejection

	Immediate (<1 week)	Early (1–4 weeks)	Late (>1 month)
Vascular	renal vein thrombosis renal artery thrombosis	renal vein thrombosis	renal artery stenosis
Parenchymal	ATN hyperacute rejection accelerated acute rejection acute rejection	acute rejection	acute rejection chronic rejection cyclosporine toxicity infection recurrent ESRD
Urologic	ureteral edema/obstruction	urinary leak/fistula/urinoma	ureteral strictures
Collections	bleeding abscess	urinoma	lymphocele
Tumors			dermatologic cancers lymphomas PTLD
Iatrogenic	bleeding/hematoma arteriovenous fistulas pseudoaneurysms		

ESRD = End-stage renal disease; PTLD = posttransplant lymphoproliferative

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Pseudorejection and True Rejection after Kidney Transplantation: Classification and Clinical Significance

Delayed graft function

- Delayed graft function (DGF) is most commonly defined as the need for at least one dialysis treatment within the first week after transplantation.
- It has also been variably defined as low or absent urine output immediately after kidney transplantation or failure of the serum creatinine to decline by more than 25 percent within 24 hours of transplant surgery.

Delayed graft function

- None of these definitions are perfect, as some patients with "slow graft function" avoid the need for dialysis, while others need dialysis for the management of refractory hyperkalemia or pulmonary edema early posttransplantation despite having prompt urine output.

EVALUATION OF ACUTE ALLOGRAFT DYSFUNCTION

- Our approach to the evaluation and diagnosis of acute kidney allograft dysfunction depends upon the timing of presentation.
- A diagnosis can be established in most patients by means of thorough history and physical examination, laboratory and imaging studies, and/or a kidney allograft biopsy.

Allograft dysfunction immediately (<1 week) posttransplantation

- Patients who develop acute kidney allograft dysfunction within the first week posttransplantation most commonly present with low urine output or failure of the serum creatinine to decrease after transplantation.
- Some patients may require dialysis in the first week after transplantation.
- Such patients are considered to have delayed graft function (DGF).

SURGICAL COMPLICATIONS OF KIDNEY TRANSPLANTATION

- The clinical presentation of surgical and nonsurgical complications of kidney transplantation may be similar.
- Graft dysfunction may reflect rejection or a urine leak; fever and graft tenderness may reflect wound infection or rejection.
- Post-transplantation events have a broad differential diagnosis that must include technical complications of surgery as well as immunologic and other causes.

SURGICAL COMPLICATIONS OF KIDNEY TRANSPLANTATION

- The fundamental algorithm in the management of post-transplantation graft dysfunction requires that vascular and urologic causes of graft dysfunction be ruled out before concluding that an event is a result of a medical cause such as rejection or cyclosporine toxicity.

SURGICAL COMPLICATIONS OF KIDNEY TRANSPLANTATION

1. Wound Infection
2. Lymphocele
3. Bleeding
4. Thrombosis
   - Renal Artery Thrombosis
   - Renal Vein Thrombosis
   - Deep Vein Thrombosis
5. Renal Artery Stenosis
6. Urine Leaks
7. Urinary Obstruction
8. Gastrointestinal Complications

Patients with Slow Recovery of Graft Function

- Patients with SGF are generally nonoliguric and experience a slow decline in serum creatinine levels.
- These patients usually do not require dialysis support but require careful attention to fluid management.
- Volume depletion must be avoided to prevent precipitation of AKI.

Patients with Slow Recovery of Graft Function

- In contrast, overzealous fluid replacement in patients with slow graft function may result in overt pulmonary edema and the need for dialysis.
- The serum creatinine of patients with slow graft function generally does not normalize within the first postoperative week.
- Nonetheless, most patients can be discharged on postoperative day 5 to 7 with close outpatient follow-up.

Patients with Delayed Graft Function

- The incidence of DGF may range from 10% to 50% and can often be anticipated based on both recipient and donor factors.
- Most patients with DGF are oliguric or anuric.
- Knowledge of the patient‘s native urine output is critical to assess the origin of the early urine output.

Patients with Delayed Graft Function

- When the transplant is from a living donor, postoperative oliguria is rare because of the short cold ischemia time.
- Nonetheless, if postoperative oliguria does occur, complications with vascular revascularization must be urgently considered.

Patients with Delayed Graft Function

- In contrast, when a patient receives a deceased donor kidney from a marginal donor kidney, DGF may be anticipated.
- The mate kidney from a deceased donor often behaves in a similar manner, and information on its function can be useful.
- Anuria refers to negligible urine production.
- Oliguria in the peritransplant period typically refers to a urine output of less than 50 mL/hour.

TABLE 10.3 Risk Factors for Delayed Graft Function due to Acute Tubular Necrosis in Deceased Donor Kidney Transplantation*

Donor Factors	Recipient Factors
Premorbid Factors and Preoperative Donor Characteristics	**Premorbid Factors**
Kidney Donor Profile Index (KDPI) > 85% (see text). The donor characteristics used to calculate KDPI include the following:	Age
Age	African Americans (compared to Whites)
Height	Peripheral vascular disease
Weight	Dialysis duration before transplant
Ethnicity	Hemodialysis (compared to peritoneal dialysis)
History of HTN	Presensitization (PRA > 50%)
History of diabetes	Reallograft transplant
Cause of death (CVA/stroke, head trauma, anoxia, CNS tumor, other)	Obesity (body mass index > 30 kg/m^2)
Serum creatinine	Hypercoagulability state†
HCV status	**Perioperative and Postoperative Factors**
Donation after cardiac death status	Hypotension, shock
Donor macrovascular or microvascular disease	Recipient volume contraction
Brain-death stress	Early high-dose calcineurin inhibitors
Prolonged use of vasopressors	mTOR inhibitors‡ (sirolimus and everolimus)
Preprocurement ATN	
Nephrotoxic agent exposure	
Organ Procurement Surgery	
Hypotension prior to cross-clamping of aorta	
Traction on renal vasculatures	
Cold storage flushing solutions	
Kidney Preservation	
Prolonged warm ischemia time	
Prolonged cold ischemia time	
Cold storage vs. machine perfusion	
Intraoperative Factors	
Intraoperative hemodynamic instability	
Prolonged rewarmed time (anastomotic time)	

Handbook of Kidney Transplantation
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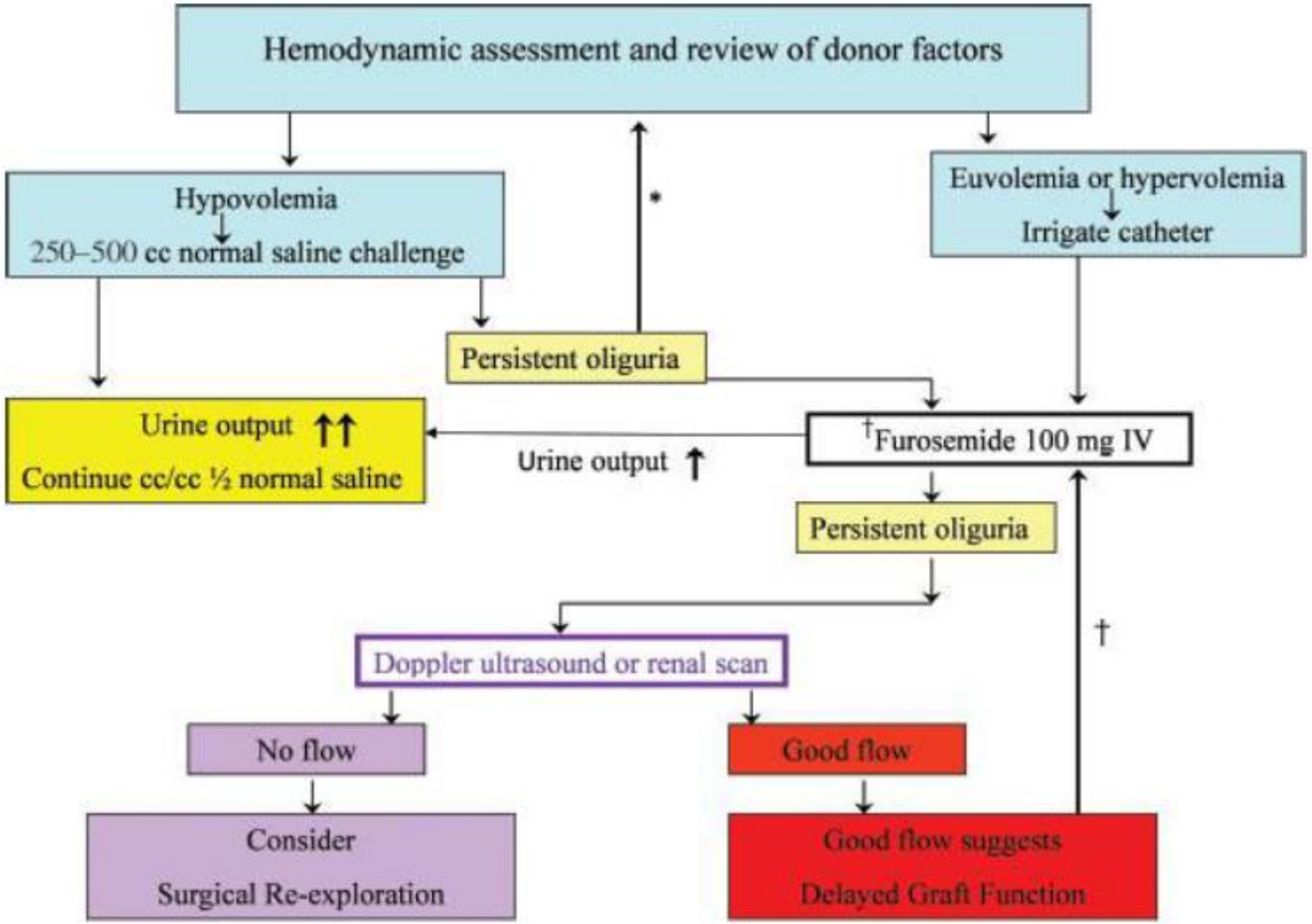

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FIGURE 10.1 Suggested algorithmic approach to postoperative fluid management in an oliguric patient. *The volume challenge can be repeated after careful assessment of the volume status and fluid balance. †Repeated doses (or furosemide drips) may be effective in patients whose urine output fluctuates. Consider switching to IV bumetanide. Persistent oliguria will usually not respond to repeated doses.

TABLE 10.2 General Guidelines for Fluid Management

1. In the euvolemic patient, urine output should be replaced hourly with ½ NS cc per cc up to 200 cc. If the urine volume is greater than 200 cc/h, give 200 cc + ½ cc for each cc > 200.
2. Other fluid and electrolyte replacement will be determined appropriately for each individual patient after clinical assessment of volume status.
3. All fluids to be replaced by IV until oral fluids are reestablished by the surgeon.
4. Fluid management for diabetic transplant recipients:
   Replace insensible loss with ½ NS
   Replace other output with ½ NS

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Initial Approach

- First obtain a history and perform a physical examination to assess for fluid balance, blood loss, or intraoperative hypotension.
- Next determine if the Foley catheter is obstructed by visual inspection and irrigation or by replacing the catheter.

Initial Approach

- Administer a 500 mL bolus of isotonic saline as a fluid challenge and give one to two doses of intravenous (IV) furosemide to try to increase urine output.
- We typically give 100 mg of furosemide to recipients of a deceased-donor transplant and 20 mg to recipients of a living-donor transplant.
- In patients with hypervolemia, give IV furosemide without a fluid challenge.

Initial Approach

- Test for the presence and strength/titer of donor-specific antibodies (DSAs).
- Obtain a kidney ultrasound with Doppler and a radionuclide renal scan to rule out obstruction, vascular thrombosis, and a urinary leak.
- However, some clinicians prefer to obtain only a kidney ultrasound without a radionuclide renal scan and measure fluid creatinine levels from an indwelling surgical drain or from fluid collections that may be seen with an ultrasound.

Subsequent Approach

- In patients who are found to have an abnormality on either kidney ultrasound or renal scan that likely explains the allograft dysfunction (eg, vascular thrombosis, urinary leak, or obstruction), treat with the appropriate therapy (eg, surgical exploration for arterial or venous thrombosis or urinary leak) and monitor serum creatinine levels and urine output.
- If the serum creatinine and urine output improve, resume routine monitoring of the patient.

Subsequent Approach

- If the serum creatinine and urine output fail to improve despite initial successful therapy of the abnormality, obtain a kidney allograft biopsy.
- In patients who have no abnormalities on either kidney ultrasound or renal scan and have no evidence of new or increasing strength/titer DSAs, the most likely cause of allograft dysfunction is postischemic ATN.

Subsequent Approach

- A biopsy may still be obtained immediately depending upon the clinical scenario (especially in highly sensitized patients or those with preformed DSA) and prebiopsy probability of identifying an unexpected cause of dysfunction.
- In most patients, monitor serum creatinine levels and urine output daily for up to one week.

Subsequent Approach

- If the serum creatinine and urine output fail to improve after one week, we obtain a kidney allograft biopsy, although some clinicians choose to repeat a renal scan and kidney ultrasound prior to obtaining a kidney biopsy.

Subsequent Approach

- A kidney biopsy is required to evaluate for acute rejection and other possible etiologies of allograft dysfunction, including early recurrent disease (eg, focal segmental glomerulosclerosis [FSGS]), oxalate deposition, and thrombotic microangiopathy.
- In addition to a biopsy, clinicians may be testing for the presence of non-human leukocyte antigen (HLA) antibodies (such as anti-angiotensin II type 1 receptor (AT1R) or antiendothelial antibodies), if available.

Subsequent Approach

- In patients who have no abnormalities on either kidney ultrasound or renal scan and are found to have a new or increasing strength/titer DSA, we obtain a kidney allograft biopsy immediately to evaluate for active antibody-mediated rejection (ABMR).

Allograft dysfunction >1 week posttransplantation

- In kidney transplant recipients who present after the first week posttransplantation with a new increase in serum creatinine of ≥25 percent from baseline or a serum creatinine that is higher than expected (such as in recently transplanted patients whose serum creatinine is continuing to decrease after transplantation), perform the following initial evaluation:

Allograft dysfunction >1 week posttransplantation

- Assessment for fever and/or abdominal symptoms and signs (eg, abdominal pain or discomfort, graft tenderness, drainage at the site of the surgical wound).
- In patients who have fever, abdominal pain, or graft tenderness, evaluate for pyelonephritis and treat with antibiotics if evidence of infection is present.
- Repeat serum creatinine upon completion of antibiotic treatment.

Allograft dysfunction >1 week posttransplantation

- Assessment of volume status.
- Increase oral hydration and repeat serum creatinine in one day.
- If the patient has symptoms and/or signs suggestive of more severe hypovolemia (eg, orthostasis) or is unable to tolerate an increase in oral fluids (eg, due to nausea and vomiting), administer a 500 to 1000 mL bolus of IV isotonic saline

Allograft dysfunction >1 week posttransplantation

- Assessment of medication history, including adherence, recently added medications (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], nondihydropyridine calcium channel blockers, azole antifungal agents), and recent changes in medication dosing.
- Assessment of dietary habits, such as drinking grapefruit juice.
- In patients with a history of recently added medications or changes in medication dosing, discontinue potential offending agents and repeat serum creatinine in two to three days.

Allograft dysfunction >1 week posttransplantation

- Measurement of blood tacrolimus (or cyclosporine) concentration.
- In patients with a blood tacrolimus (or cyclosporine) concentration above the therapeutic range, reduce the dose of the calcineurin inhibitor until bring it to therapeutic range and repeat the serum creatinine and blood tacrolimus (or cyclosporine) concentration in two to three days.
- It should be noted that calcineurin inhibitor toxicity may occur at blood concentrations that are within the target range.

Allograft dysfunction >1 week posttransplantation

- Assessment for the presence and strength/titer of DSAs.
- In patients with a de novo DSA or patients with a preexisting DSA before transplantation who develop a significant rise in DSA titer, perform a kidney allograft biopsy to evaluate for ABMR.

Allograft dysfunction >1 week posttransplantation

- Measurement of plasma donor-derived cell-free DNA (dd-cfDNA) level, a biomarker for the detection of acute allograft rejection.
- However, practice may vary at other transplant centers.
- Some centers do not yet routinely measure plasma dd-cfDNA levels, while other centers do not begin checking plasma dd-cfDNA levels until after one month posttransplantation.
- In patients with a plasma dd-cfDNA level >1 percent or a rising trend in serial dd-cfDNA measurements, perform a kidney allograft biopsy to evaluate for acute rejection.

Allograft dysfunction >1 week posttransplantation

- Measurement of blood BK polyomavirus (BKPyV) and cytomegalovirus (CMV) viral loads.
- In patients with a plasma BKPyV viral load ≥10,000 copies/mL, a presumptive diagnosis of BKPyV-associated nephropathy (BKPyVAN) is frequently made if no other causes of allograft dysfunction are identified.

Allograft dysfunction >1 week posttransplantation

- Reduce immunosuppression and monitor viral loads every two to four weeks thereafter, when the clinical picture suggests that BKPyVAN is the most likely cause.
- However, if the cause of allograft dysfunction is uncertain or kidney function impairment and/or viremia fail to resolve despite reducing immunosuppression, perform a kidney allograft biopsy.

Allograft dysfunction >1 week posttransplantation

- Assessment of characteristics of the donor (eg, cause of death [for deceased donors], age, history of hypertension, history of tobacco use) and the donor kidney (eg, estimated glomerular filtration rate [eGFR] at the time of recovering the kidney, kidney weight, kidney donor profile index [KDPI], kidney biopsy findings).

Allograft dysfunction >1 week posttransplantation

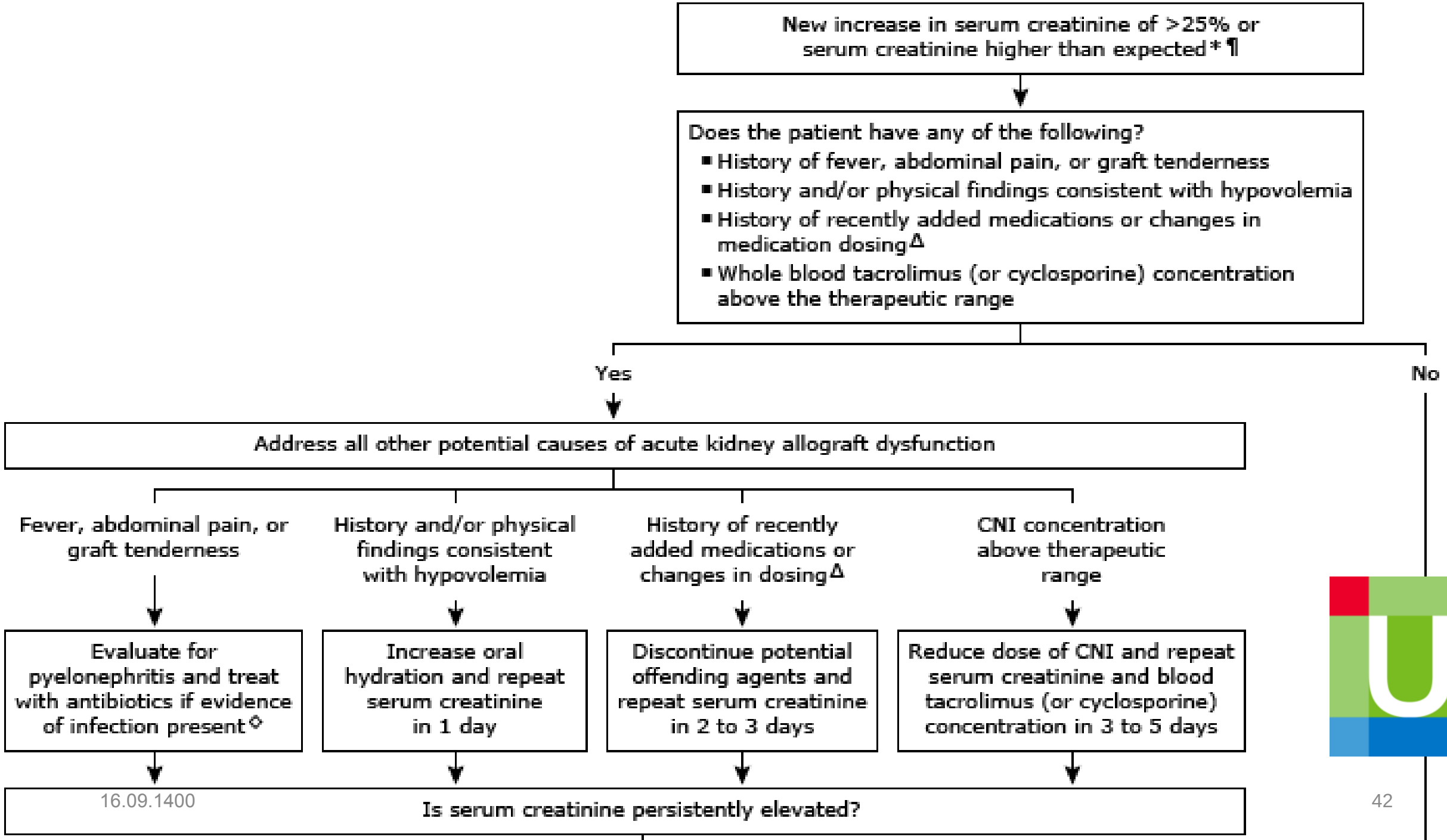
- Assessment of the function of the "mate kidney" (ie, the contralateral kidney of the deceased donor, if also recovered for transplant) and comparison with that of the recipient with allograft dysfunction.

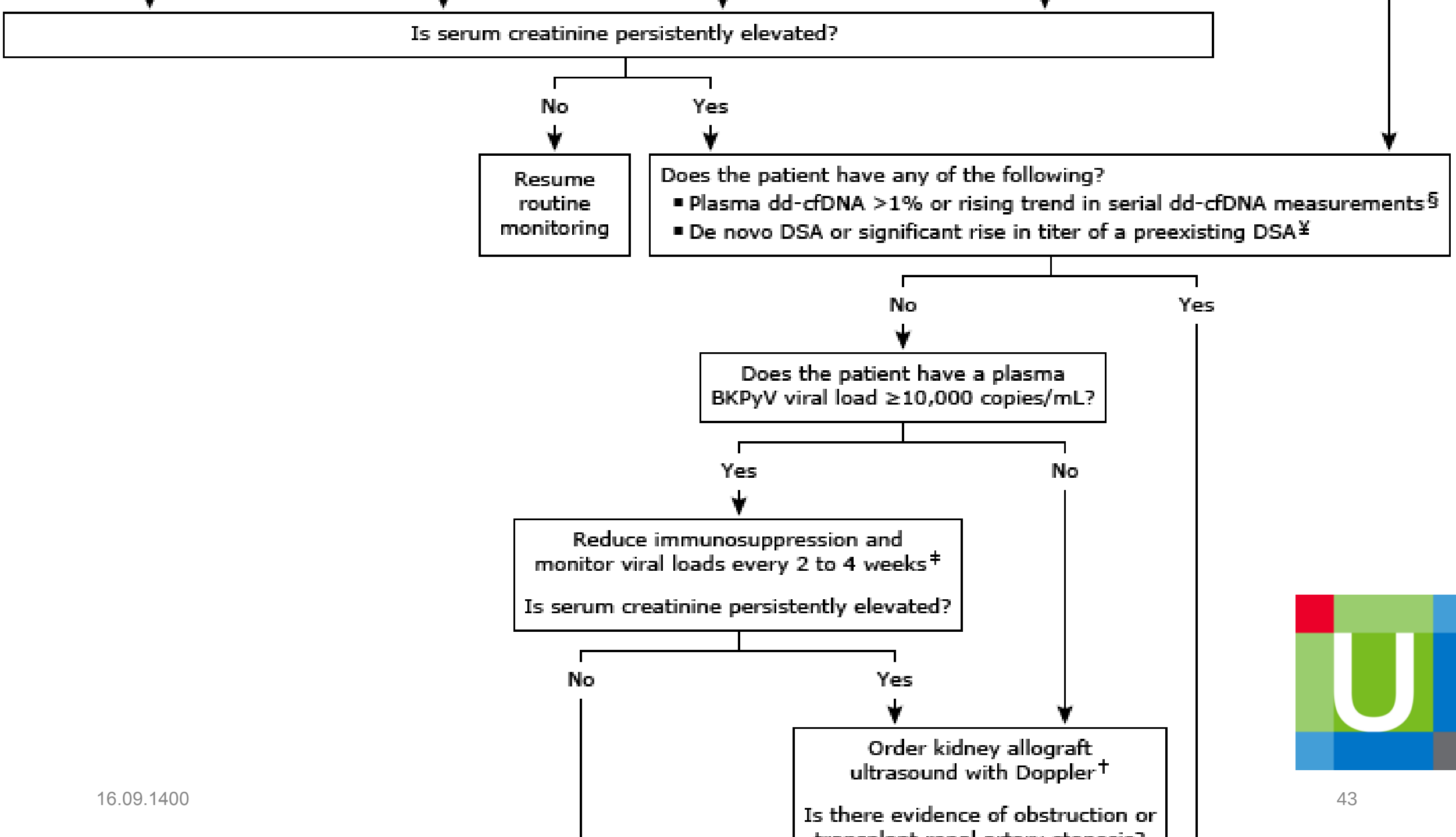
Patients presenting with proteinuria

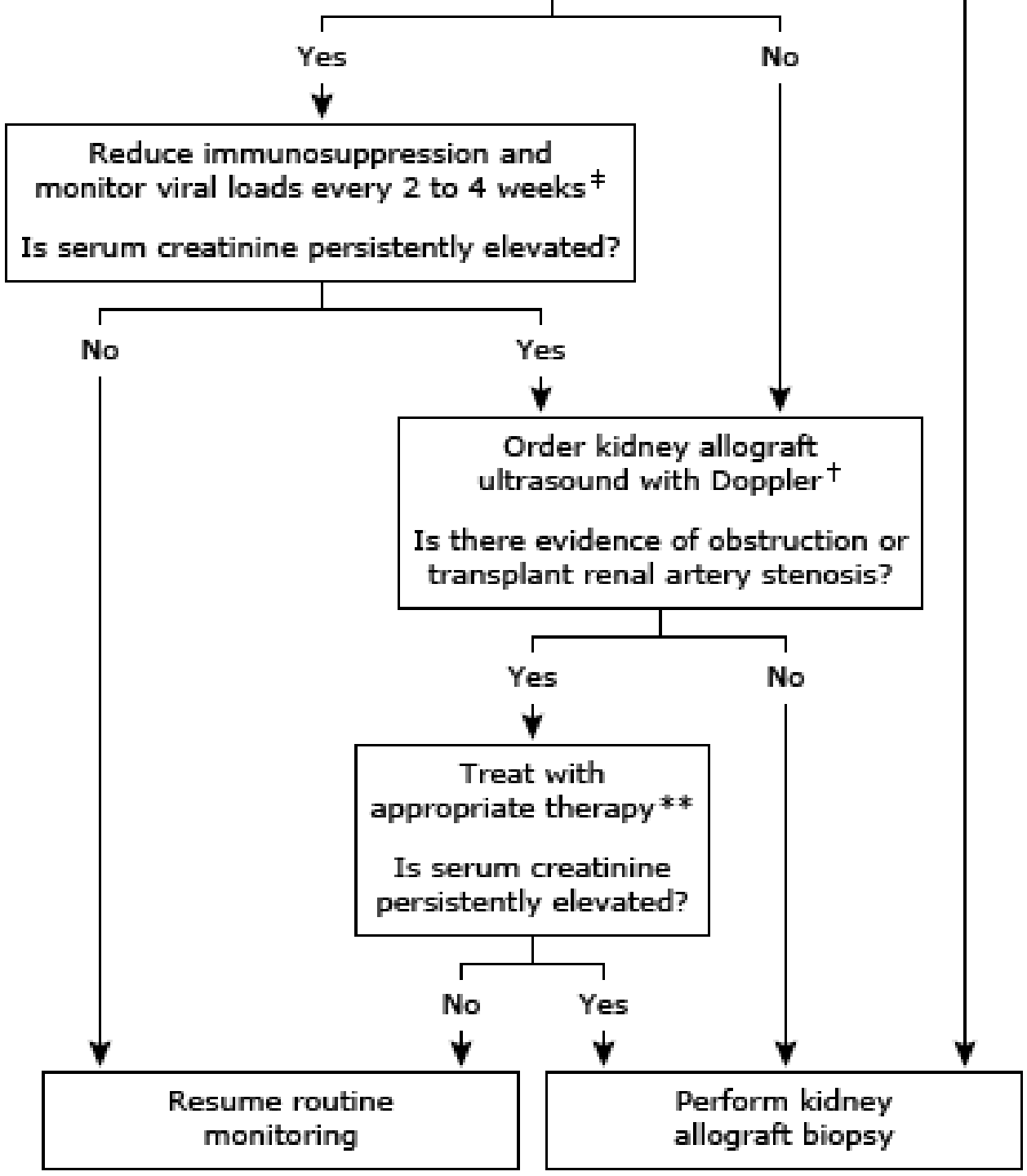
- Proteinuria in transplant recipients may originate from either the native kidneys or the allograft.
- Proteinuria derived from native kidneys generally dissipates over time posttransplantation as the end-stage kidneys undergo progressive sclerosis.
- New or increasing proteinuria greater than 1 g/day after transplantation is indicative of allograft dysfunction.

Patients presenting with proteinuria

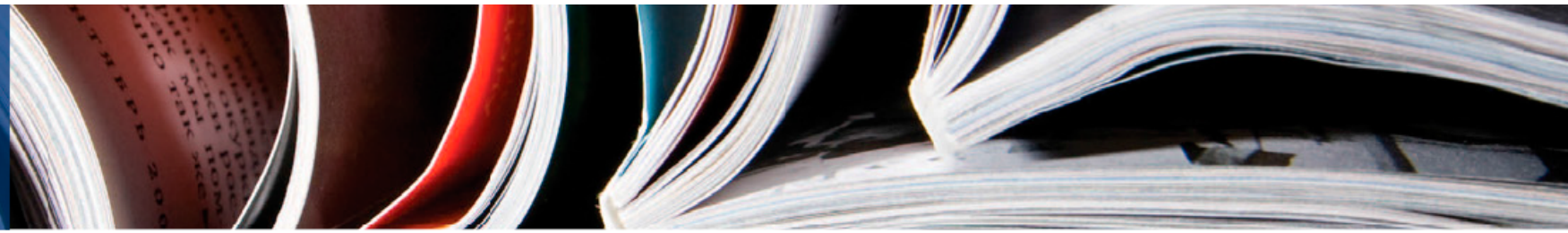
- The differential diagnosis for proteinuria after kidney transplantation includes recurrent glomerular disease, ABMR, chronic allograft nephropathy (CAN), and de novo glomerulopathies.
- Generally perform a kidney allograft biopsy in all kidney transplant recipients who present with proteinuria greater than 1 g/day, regardless of the serum creatinine concentration, if not otherwise contraindicated.


New increase in serum creatinine of >25% or serum creatinine higher than expected*¶
Does the patient have any of the following?
History of fever, abdominal pain, or graft tenderness
History and/or physical findings consistent with hypovolemia
History of recently added medications or changes in medication dosing Δ
Whole blood tacrolimus (or cyclosporine) concentration above the therapeutic range
Yes
No
Address all other potential causes of acute kidney allograft dysfunction
Fever, abdominal pain, or graft tenderness
History and/or physical findings consistent with hypovolemia
History of recently added medications or changes in dosing Δ
CNI concentration above therapeutic range
Evaluate for pyelonephritis and treat with antibiotics if evidence of infection present◇
Increase oral hydration and repeat serum creatinine in 1 day
Discontinue potential offending agents and repeat serum creatinine in 2 to 3 days
Reduce dose of CNI and repeat serum creatinine and blood tacrolimus (or cyclosporine) concentration in 3 to 5 days
Is serum creatinine persistently elevated?


Is serum creatinine persistently elevated?
No
Yes
Resume routine monitoring
Does the patient have any of the following?
Plasma dd-cfDNA >1% or rising trend in serial dd-cfDNA measurements§
De novo DSA or significant rise in titer of a preexisting DSA¥
No
Yes
Does the patient have a plasma BKPyV viral load ≥10,000 copies/mL?
Yes
No
Reduce immunosuppression and monitor viral loads every 2 to 4 weeks‡
Is serum creatinine persistently elevated?
No
Yes
Order kidney allograft ultrasound with Doppler†
Is there evidence of obstruction or


Yes
No
Reduce immunosuppression and monitor viral loads every 2 to 4 weeks‡
Is serum creatinine persistently elevated?
No
Yes
Order kidney allograft ultrasound with Doppler†
Is there evidence of obstruction or transplant renal artery stenosis?
Yes
No
Treat with appropriate therapy**
Is serum creatinine persistently elevated?
No
Yes
Resume routine monitoring
Perform kidney allograft biopsy

REVIEW



Evaluation and Treatment of Acute Rejection in Kidney Allografts

James E. Cooper

Abstract

Advances in immunosuppressive therapy have drastically improved acute rejection rates in kidney transplant recipients over the past five decades. Nevertheless, it should remain high on any differential diagnosis of unexplained graft dysfunction because of the potential negative effect on graft longevity. Understanding the pre- and post-transplant risk factors for acute rejection can help estimate the probability of immunologic graft damage, and accurate identification of the type and severity of acute rejection will guide appropriate treatment. Tissue biopsy remains the gold standard for evaluating immunologic graft damage, and the histologic definition of acute rejection has evolved in recent years. Intravenous steroids and T cell depletion remain the standard therapy for T cell–mediated rejection and are effective in reversing most cases. Plasma exchange and intravenous Ig, with or without rituximab, are most commonly used for the treatment of antibody-mediated rejection and several newer agents have recently been investigated for severe cases. This review aims to provide the general nephrologist caring for transplant recipients with an approach to immunologic risk assessment and a summary of recent advances in the diagnosis and treatment of acute graft rejection.

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Table 2. Treatment options for acute allograft rejection

Treatment	Indication	Mechanism	Adverse Effects
Methylprednisolone	TCR: Banff Ia, Ib	Multiple, anti-inflammatory glucocorticoid	Hyperglycemia, hypertension, other metabolic effects
rATG	TCR: Banff Ib, IIa, IIb, III	T cell depletion	Fever, chills, hypertension, hypotension, leukopenia, infusion reaction, serum sickness
Plasma exchange	AMR	Antibody removal	Fever[a], chills[a], urticaria[a], TRALI[a], bleeding
IVIG	AMR	Multiple "immunomodulatory" effects including antibody clearance, neutralization, and inhibited production, Fc receptor saturation, complement inhibition	Infusion reaction including headache, fever, chills, urticaria, back pain, abdominal pain, nausea, vomiting
Rituximab	AMR	Anti-CD20 B cell depletion	Infusion reaction, HBV reactivation, PML
Bortezomib	AMR	Plasma cell apoptosis *via* proteasome inhibition	Peripheral neuropathy, fatigue, generalized weakness
Eculizumab	AMR	Terminal complement C5 inhibition	Meningococcal infection, influenza, peritonitis
C1-INH	AMR	Classic complement pathway inhibition	Headache

TCR, T cell–mediated rejection; rATG, rabbit anti-thymocyte globulin; AMR, antibody-mediated rejection; TRALI, transfusion-related acute lung injury; IVIG, intravenous immunoglobulin; HBV, hepatitis B virus; PML, progressive multifocal leukoencephalopathy; C1-INH, C1-esterase inhibitors.

[a]Associated more with plasma as replacement fluid.

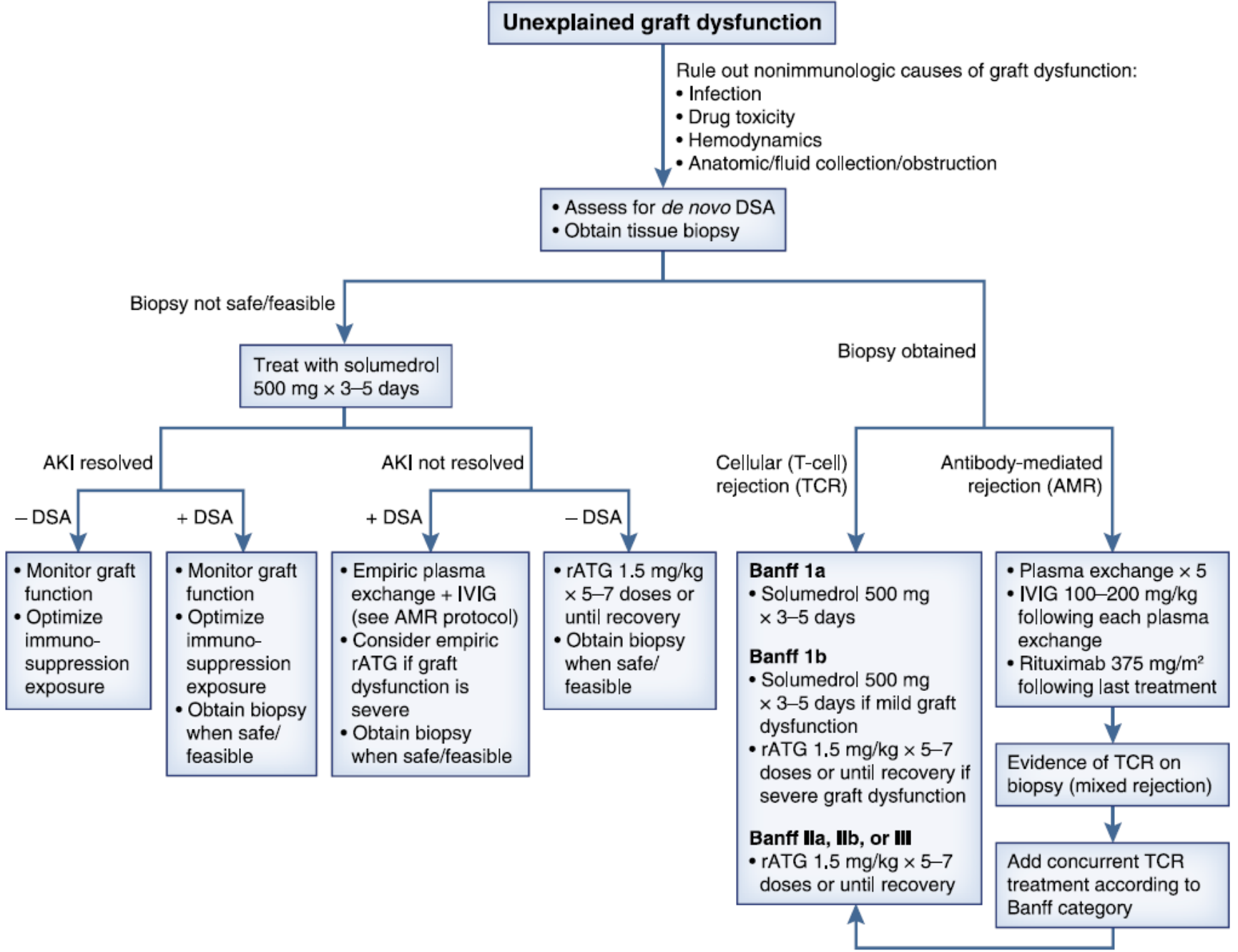

Figure 3. | Proposed algorithm for treatment of presumed and biopsy-proven acute kidney allograft rejection. Once non-immunologic

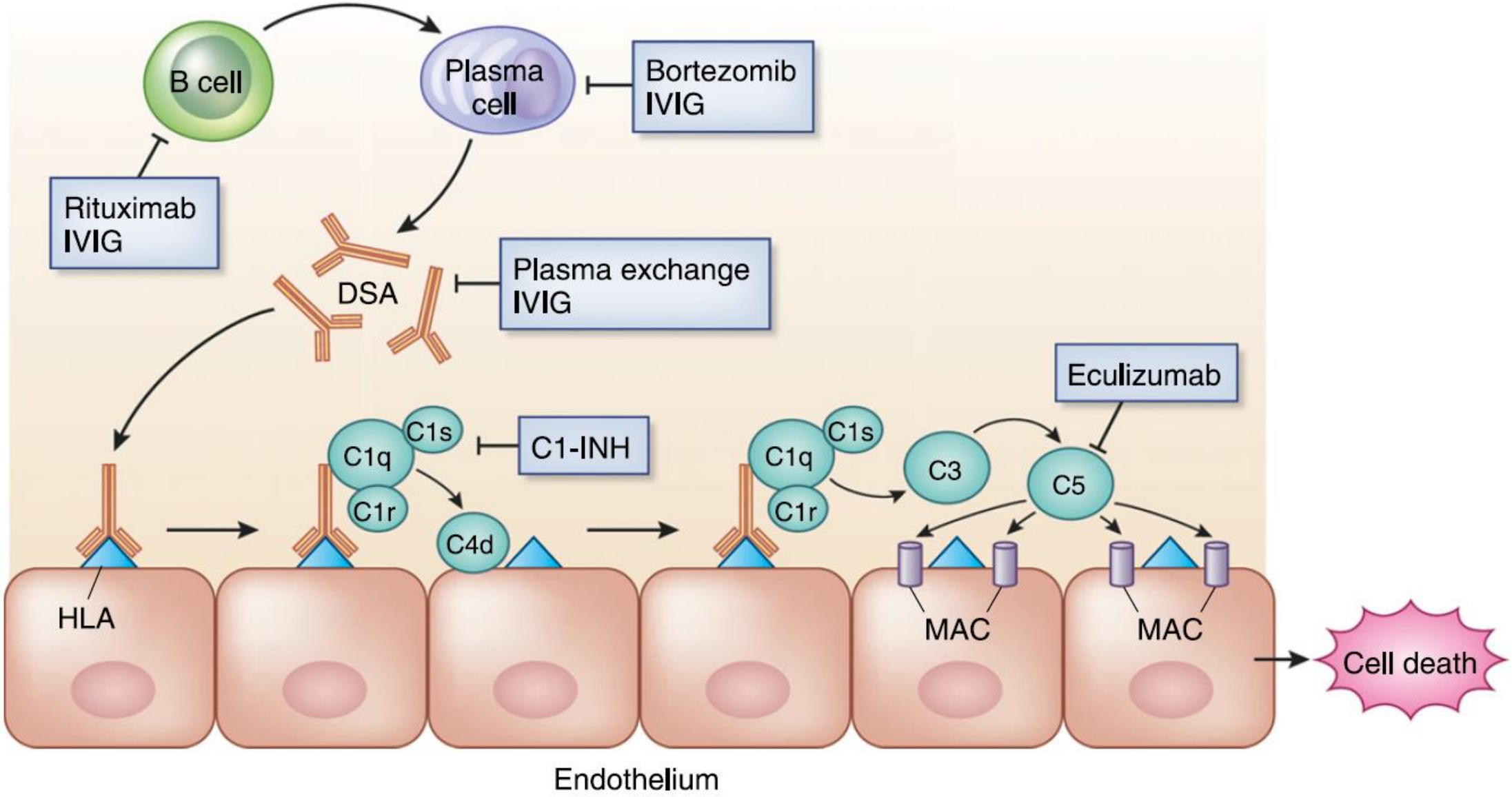

Figure 4. | **Target sites for current available and experimental therapeutic agents for antibody-mediated allograft rejection.** B cells (inhibited by rituximab) differentiate to plasma cells (inhibited by bortezomib), which generate donor-specific anti-HLA antibodies (removed by plasma exchange, modulated by IVIG). Upon binding to HLA molecules on graft endothelium, donor-specific antibodies (DSA) fix complement (inhibited by C1-esterase inhibitors [C1-INH]) and initiate a cascade resulting in C5 cleavage (inhibited by eculizumab) and formation of the