Transplant emergencies

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ED visits are common after kidney transplant

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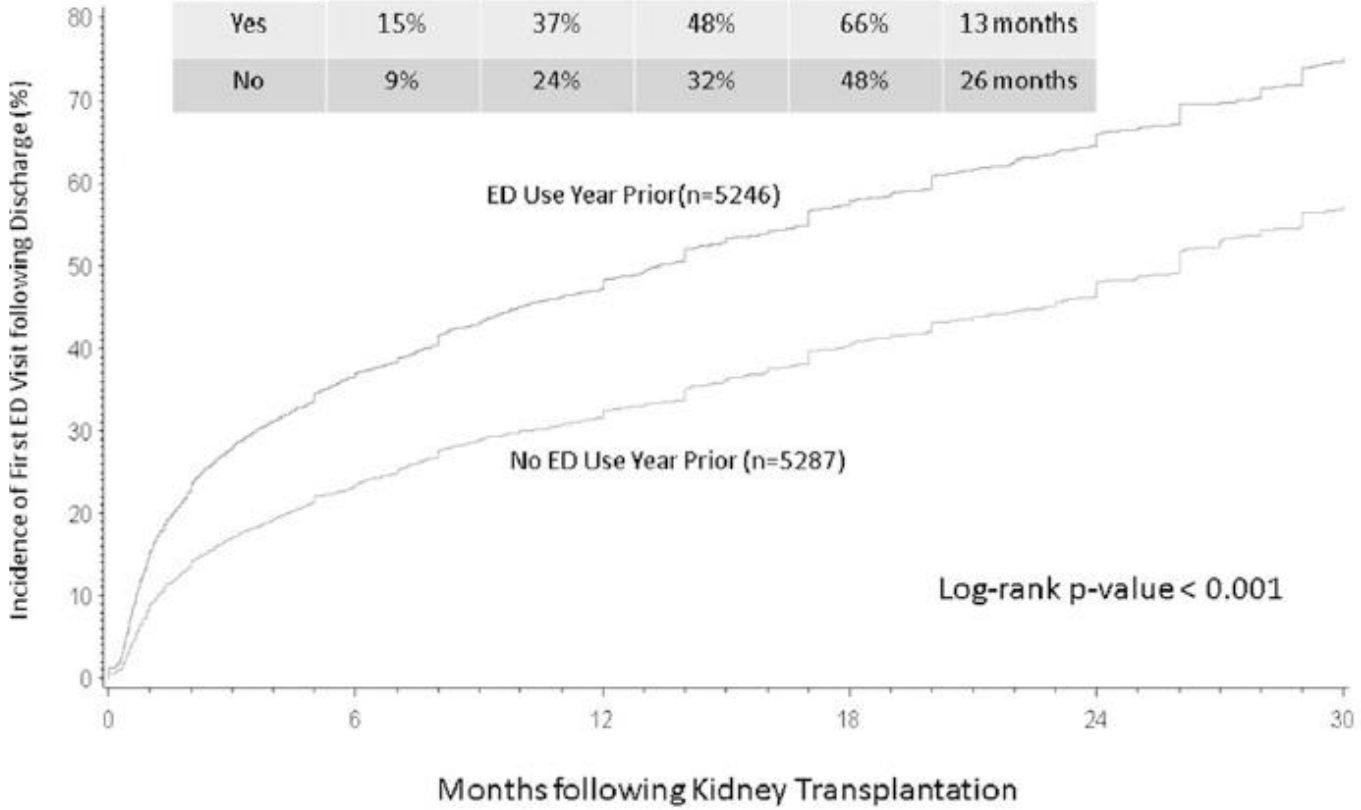
ED Use Year Prior to Transplant	Incidence of First ED Visit Following Discharge for Kidney Transplantation(%)				Median time to first ED Visit
	1 month	6 months	12 months	24 months	
Yes	15%	37%	48%	66%	13 months
No	9%	24%	32%	48%	26 months



KTRs from NY, FL, CA, 2009-2012

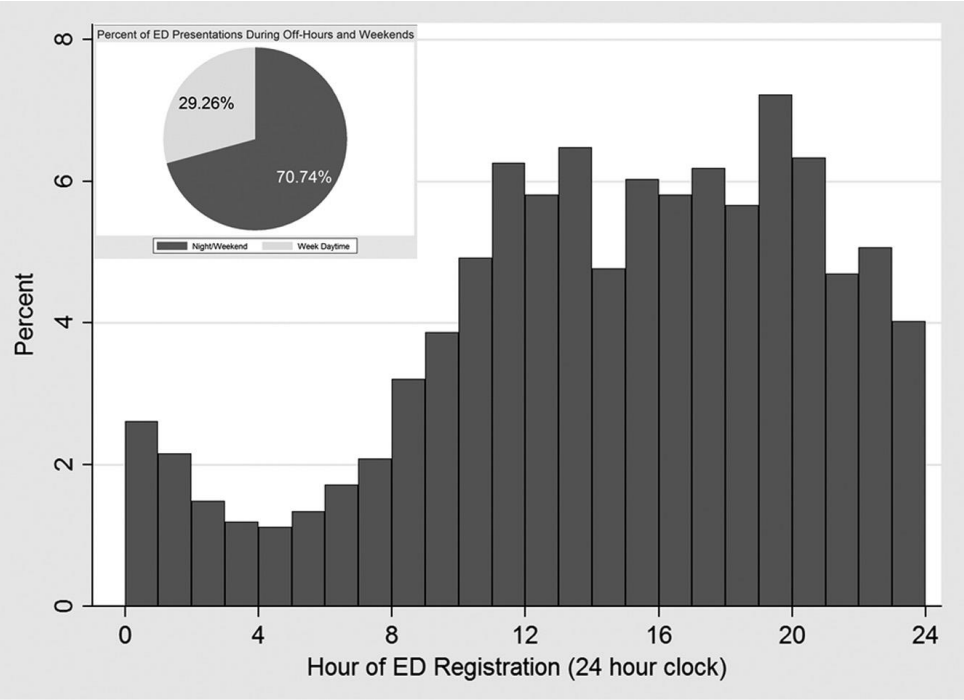
Schold et al. CJASN 11:674-683, 2016.

Cumulative incidence of ER visits at 1/12/24 months 12%/40%/57%.
More frequent among:

- Women
- Younger age
- Hispanics
- African-Americans
- Public insurance
- Diabetes
- PVD
- ER use prior to transplant

48% of visits led to admission
Rate of visits not correlated with center volume

ED visits for transplant recipients occur at all hours of the day

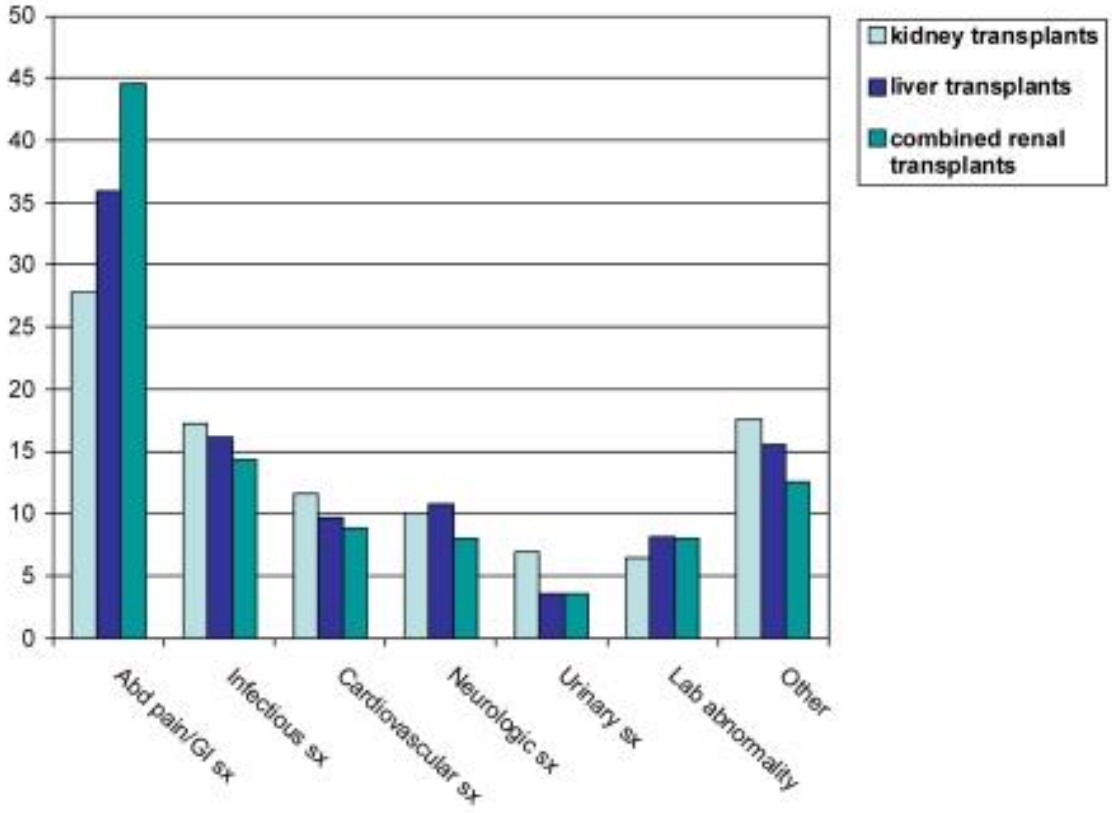


- 33% of kidney and 60% of pancreas recipients had ED visit
- 45% of visits occurred in first 60 days after transplant
- 72% of visits led to admission (76% for SPK)
- 42% of admissions were < 24 hours, 33% 1-3 days

1900 abdominal SOTRs at Northwestern – access to on-call transplant clinician 24/7
56% of visits occurred during transplant clinic hours

McElroy et al. Transplantation 99:1652-1657, 2015.

Why do transplant recipients seek care in the ED?



Presenting complaints:

- GI symptoms: N/V/D, abdominal pain, GIB
- Infectious symptoms: fever, wound infection, abscess, presumed bacteremia
- Cardiac symptoms: dyspnea, edema, chest pain, HTN
- Urinary symptoms: dysuria, hematuria, urgency, frequency
- Neurologic symptoms: dizziness, weakness, neurologic deficits

568 pts (378 KT, 153 LT, 37 kidney + other – 1251 ED visits, 2000-2004, UIC,

Unterman et al. Western Journal of Emergency Medicine 10:4854, 2009.

- You *shouldn’t* get called much from the ED about transplant patients (transplant service pager 87777; Epic “Nephrology-Transplant Consult”)
- The reasons why you will get called about transplant patients aren’t necessarily the same as the reasons why patients are evaluated in the ED.

It’s 3 a.m., why are you calling me?

- Abnormal lab values
  - Electrolytes and glucose
  - Blood counts
  - “Panic value” drug levels
- Real symptoms
  - Urinary symptoms
  - Fevers
  - Gout attack
  - Other
- Medication questions

Hyperkalemia

- Common, especially early on after transplant
  - Medication effects:
    - Calcineurin inhibitors (↓renin/aldosterone, ↓ responsiveness to aldosterone)
    - Bactrim (trimethoprim inhibits potassium secretion from ENaC)
    - Beta-blockers (↓ renin release; ↓ cellular uptake of potassium)
  - Hyperglycemia
  - Metabolic acidosis
  - Slow graft function
  - Dietary indiscretion (aka dialysis liberation syndrome): no more HD ≠ no more HD diet

Bantle et al. Arch Intern Med 145:505-508, 1985.
Choi et al. N Engl j Med 328:703-706, 1993.
McCauley et al. Am J Nephrol 22:347-351, 2002.

Management of hyperkalemia

- High threshold for sending transplant patients to the ED, due to the possibility of prolonged exposure to infectious diseases and/or mismanagement in the ED.
  - Anyone with a K ≥ 7 should be sent to the ED.
  - For values between 6-7, see if the patient has a K binder or Lasix at home, or if they have a pharmacy close by to call in a prescription
    - Avoid K binders if patients still have post-operative ileus
  - Can hold Bactrim temporarily
  - Can adjust insulin if markedly hyperglycemic
  - Reinforce dietary potassium restriction
- Chronic management may include thiazide or loop diuretics, fludrocortisone, switching Bactrim to alternative agent for PCP prophylaxis (dapsone or atovaquone), or K binder

Zaidan et al. Kidney Int 84:1057-1059, 2013. Rattanavich et al. Transpl Int 32:110-111, 2019. Lim et al. Transplantation 2019

Other electrolyte disturbances

- Hypomagnesemia
  - Very common: CNIs can cause a renal magnesium leak (downregulation of TRPM6 in DCT)
  - Nothing to do acutely
  - Very difficult to replete with enough oral Mg to make magnesium normal, but low doses of Mg may be tolerated
  - K sparing diuretics may be helpful chronically
  - Hypomagnesemia linked to ↑risk of PTDM
- Hypophosphatemia
  - Very common
  - Renal phosphate leak post-transplant (persistent elevated PTH and FGF-23)
  - Very difficult to replete – high doses of oral phosphate supplement can cause CaPhos deposits in the kidney → graft dysfunction
  - Nothing to do acutely

1. Nijenhuis et al. J Am Soc Nephrol 15:549-557, 2004. 2. Huang et al. J Am Soc Nephrol 27:1793-1800, 2016. 3. Bhan et al. Kidney Int 70:1486-1494,2006. 4. Evenepoel et al. Am J Transplant 7:1193-2000, 2007.

Diabetes gone wild

- Hyperglycemia
  - Healthy kidney plays a crucial role in insulin clearance
    - Deceased insulin clearance in setting of ESRD
    - Receive kidney transplant → renal function improves → insulin clearance increases → greater insulin requirements
  - CNIs (FK>CsA) are diabetogenic
  - Some patients may still be on prednisone
  - New diagnosis of diabetes (PTDM) common after transplant – 12% in 1st 3 years if steroid-free, 18% if maintenance steroids
  - Use your medical judgment. If the patient has a markedly elevated glucose and no prior history of diabetes, refer to ED vs. next day follow up if relatively asymptomatic. If the patient is a known diabetic, insulin can be adjusted.
- Hypoglycemia
  - Most likely lab artifact

Luan et al. Transplantation 91:334-341, 2011.

Elevated BUN and/or creatinine

- Unlikely to require urgent action.
  - You are unlikely to get called with a creatinine value for a fresh transplant patient.
  - High BUN/creatinine calls will likely be either someone coming in for pretransplant evaluation (CUMC lab) or someone with a failing transplant (Quest or LabCorp)
- If it is a weekday, will be addressed by the outpatient team the next morning.
- If it is a weekend, can speak with on-call (or outpatient) nephrologist.

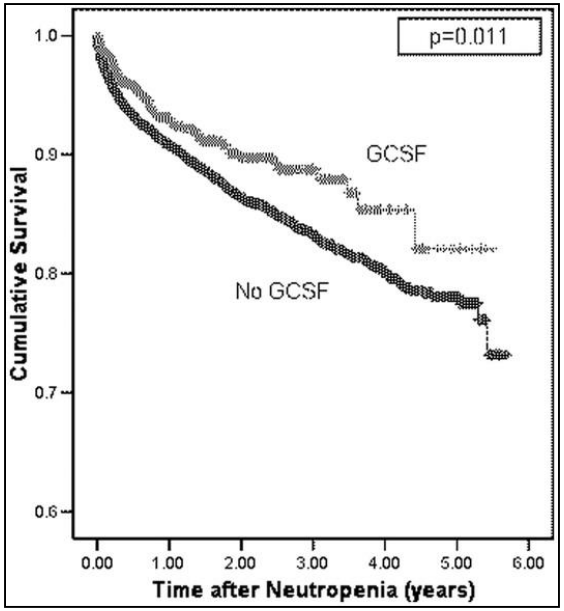
Leukopenia

- Multiple contributing factors
  - Lymphocyte-depleting antibodies: thymoglobulin, alemtuzumab
  - Maintenance immunosuppressants: mycophenolate, mTOR inhibitors
  - Adjunctive agents: rituximab
  - Prophylactic antibiotics: Valcyte, Bactrim
  - Viral infections: CMV, EBV, other
- Frequent in transplant patients, especially in the first year
  - More frequent with steroid free regimens
  - FREEDOM study: 16.5% RSW, vs. 13.% maintenance steroids at 1-year – basiliximab induction (non-lymphocyte depleting)
  - CUMC: 28-36% RSW vs. 19% maintenance steroids - thymoglobulin
  - MORE registry: 60.6% vs. 29.9% at 4 years
- Neutropenia less common than leukopenia – but still common
  - Zafrani et al.: 28% incidence of neutropenia at 1-year

Vincenti et al. Am J Transplant 8:307-316, 2008.
Ueda et al. Ann Transplant 19:84-92, 2014.
Zafrani et al. Am J Transplant 9:1816-1825, 2009.

Outpatient management of leukopenia

- Use of GCSF does not increase risk of acute rejection, does not increase risk of allograft failure, associated with lower risk of death (AHR 0.78, p=0.087)
- Adjust dose of antimetabolite and/or prophylactic antibiotics if needed
  - NYP Pharmacy guidelines: give GCSF to any SOT recipient with ANC < 1500 if otherwise would need to reduce dose of antirejection medications or antibiotics



Turgeon et al. *Transplant Infect Dis* 2:15-21, 2000.
Hurst et al. *Transplantation* 92:36-40, 2011.
https://infonet.nyp.org/pharmacy/PharmacyM/GranulocyteColonyStimulatingFacto.pdf

Leukopenia management on-call

- Leukopenia calls will likely be from Quest/Labcorp
- Patients with asymptomatic leukopenia do not require emergency management when you are on call
- Patients with fevers and neutropenia should be referred to ED
  - CUMC data: ~3% will develop febrile neutropenia in 1st year post-transplant
  - Similar to febrile neutropenia in oncology, often no organism isolated (54% no organism, 43% bacterial, 11% viral; 20% clinical infection without organism)
- You are unlikely to get prior authorization for GCSF after hours
  - If patient has GCSF at home -> can take
- Don't make any changes to antirejection medications or prophylactic antibiotics – send email to patient's nephrologist

Anemia

- Multiple common contributors:
  - Postoperative inflammation
  - Perioperative blood loss
  - Slow graft function
  - Iron deficiency
  - Bone marrow suppression (mycophenolate, Valcyte, Bactrim)
- Rarer entities:
  - Hemolytic anemia from TMA, dapsone
  - Red cell aplasia from parovirus infection
  - Severe sickle cell disease
- On-call management:
  - Nothing to do overnight unless significant change from prior

Post-transplant erythrocytosis

- Post-transplant erythrocytosis (PTE) defined as hemoglobin > 17 g/dl or hematocrit > 51%
- Prevalence of PTE 8-22%
- PTE usually diagnosed in first 8-24 months post-transplant
  - Risk factors/associations include male gender, absence of native nephrectomy, rejection-free course, smoking, PKD
- Symptoms may include headache, malaise, dizziness, ? increase risk of thromboembolic events
- Treatment goal is to get Hgb < ~17
  - ACE-I and ARB both decrease Hgb/Hct: mean change -1.2/3.5%
  - Therapeutic phlebotomy may be used in patients who do not tolerate or fail to reduce Hgb with ACE-I/ARB
- No urgent intervention needed

Malyszko et al. Transplant Int 2012;25:1013-1023.
Hiremath et al. AJT 2007;7:2350-2360.

“Panic value” drug levels

- Most likely will be from Quest/LabCorp in patient > 3 months from transplant.
- CUMC lab calls for markedly elevated tacrolimus levels (> 20)
  - Levels this high are often due to patient taking medication prior to blood draw
  - Can give P450 inducers to rapidly lower CNI levels
    - Phenobarbital and phenytoin (protect against seizures) preferred over rifampin
    - Don’t try this at home
- Outside labs may call for drug levels that are too low
  - Levels that are “low” may be what we’re aiming for (or medication may have been discontinued without changing the lab order)
- Can call/email/text patient’s nephrologist or send email to coordinators
- Do not adjust the dose unless explicitly instructed to by the patient’s nephrologist.

Hematuria and/or dysuria

- Are there any other symptoms?
  - Dysuria/hematuria, frequency, urgency, foul-smelling urine, cloudy urine
  - Fevers, graft tenderness
- How far out is the patient from transplant?
- Does the patient have a ureteral stent?
- Was the patient recently biopsied?
- Are they passing clots?
- Are they able to empty their bladder completely?
- Does the patient have polycystic kidney disease?

Hematuria and/or dysuria

- Transplantation requires a bladder incision.
- Gross hematuria is common in the first few weeks after transplant, even in patients without a ureteral stent.
- In patients who are stented, hematuria may be accompanied by irritative voiding symptoms (dysuria, urgency, frequency)
- In patients who are not stented, hematuria from something other than a UTI typically does not have other urinary symptoms unless clots are also being passed.

Hematuria and/or dysuria

- When patients have hematuria or dysuria, the two main issues are:
  - Is this a UTI?
  - What can we give for symptomatic relief?
- If there is concern for a UTI, patients should be told to come in the next day to give a urine specimen.
  - Patients need to call coordinator before coming in
  - Reasonable to prescribe empiric antibiotics (cephalosporin or fluoroquinolone if no history of resistant organisms)
  - Avoid Bactrim – patients are typically taking already for PCP prophylaxis, so high-incidence of Bactrim-resistant urinary isolates
- If there is concern for pyelonephritis, patient should be referred to the ED

Treatment of dysuria

- If you do not think they need to start antibiotics overnight, can offer medicine for symptomatic relief.
- No clinical trials in transplant patients.
  - Stents in transplant patients may cause fewer symptoms than stents in non-transplant patients.

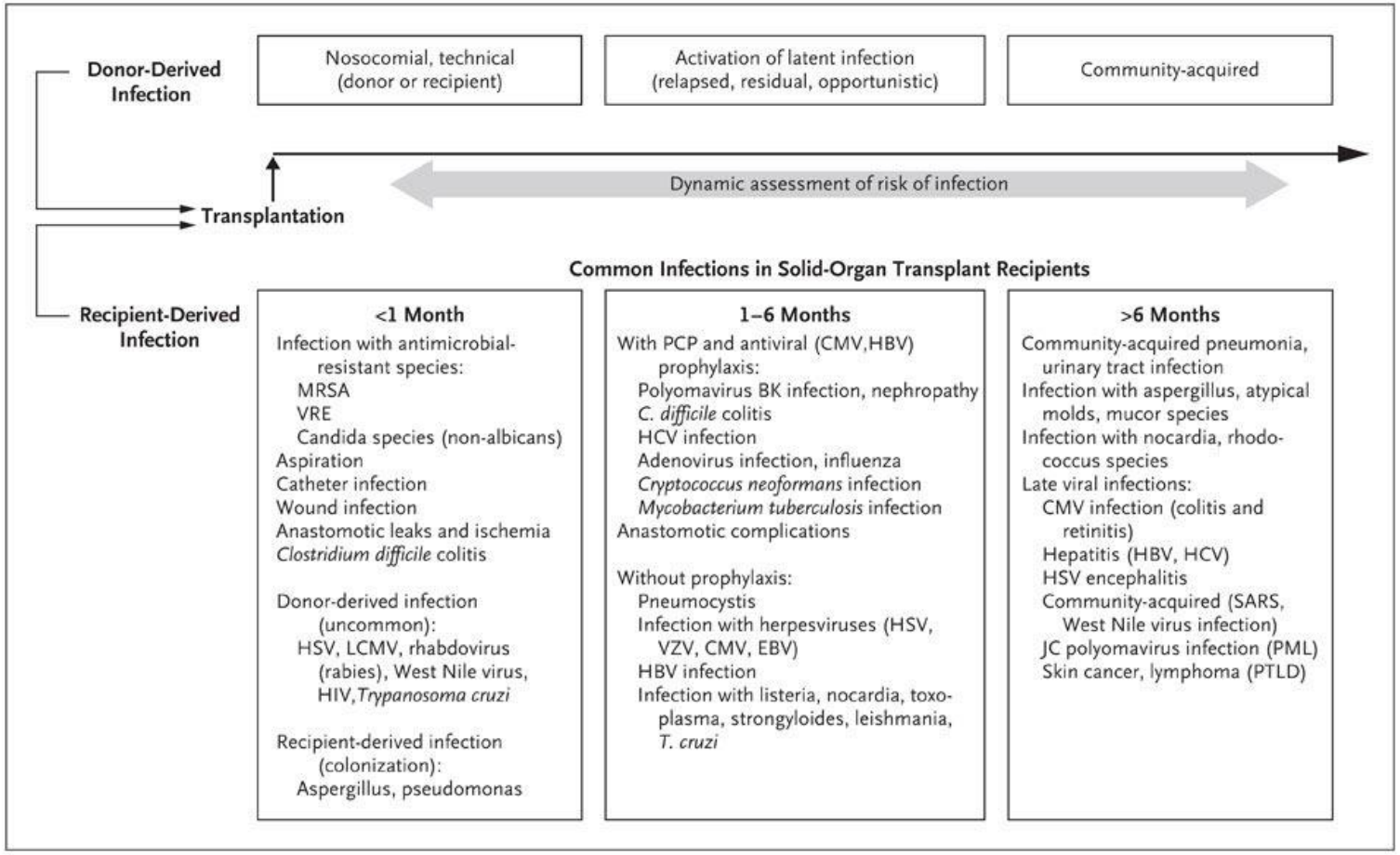
Regan et al. J Endourology 23:2047-2050, 2009.

Treatment of dysuria

- Studies in non-transplant population (ureterscopy with stone removal and stent placement) have looked at 3 classes of medications:
  - Urinary analgesics – phenazopyridine – no difference when compared with oxybutynin or placebo at day 1 and 2 and day of removal
    - Can try Pyridium 100 mg bid-tid (not recommended if CrCl < 50)
  - Anticholinergics – studies have shown benefit with tolterodine ER (Detrol), oxybutynin (Ditropan), and solifenacin (Vesicare)
    - Can try tolterodine 1 mg q12 or oxybutynin 2.5 mg q12 (tolterodine may have lower risk of dry mouth; extended-release formulations may have lower risk of side effects than immediate-release)
  - Alpha blockers – meta-analysis showed significant decrease in urinary symptoms and pain
    - Can try tamsulosin 0.4 mg daily or terazosin 2 mg daily

Norris et al. Urology 71:792-795, 2008. Yakoubi et al. J Urol 186:928-934, 2011. Park et al. J Endourol 23:1913, 2009.

Approach to fevers after transplant: changing timeline of infection



Fishman JA. *N Engl J Med* 2007;357:2601-2614.

Fever

- The most common causes of infection in our patients are urinary tract infections and viral infections.
- For patients who call up with fevers, any associated symptoms should be elicited (e.g., urinary symptoms, URI symptoms, wound drainage).
- For patients without associated symptoms, watchful waiting with Tylenol for symptoms is appropriate for most patients.

Fevers

- For patients with associated symptoms, the next step depends on the symptoms.
  - If the symptoms seem consistent with a UTI, it is reasonable to treat for acute cystitis (minimum 7-day course of antibiotics) and ask them to come in the next day to give a urine culture (high frequency of drug-resistant organisms in this population).
  - If the symptoms seem consistent with a URI, trial of OTC medications
  - If the symptoms seem concerning for pneumonia, evaluation in the ER is probably warranted.
  - If the symptoms seem concerning for a wound infection, can call the transplant PA (beeper 82729) or attending and have them contact the transplant surgical fellow to call the patient.

Gout

- High incidence of hyperuricemia and gout
  - Calcineurin-inhibitors lower GFR and increase uric acid
  - Risk greater with cyclosporine than tacrolimus
- Acute treatment can be difficult
  - NSAIDs – may be used for a few days in someone with stable and relatively normal renal function, though would avoid in first few months
  - Colchicine – dose needs to be adjusted with co-administration of p-glycoprotein inhibitor (cyclosporine; can give 0.6 mg as single dose)
  - Prednisone – can give quick taper (7-10 days); probably 1st line treatment as long as patient is not a poorly controlled diabetic
- Allopurinol and febuxostat can be used to reduce uric acid levels over long-term
  - Significant drug interaction with azathioprine

Abbott et al. Transplantation 27:1383-1391, 2005.
Vargas-Santos et al. Am J Kid Dis 70:422-439, 2017.

Other medical problems

- Diarrhea
  - Most commonly due to medications
  - Increased risk of C. difficile colitis in this population
  - Norovirus and Sapovirus also common
  - Diarrhea may be a presenting symptom of UTI/allograft pyelo
  - If no concerning symptoms (fevers, graft pain, abdominal pain, urinary symptoms), can usually wait until morning
- Headache
  - Can be side effect of medications (CNIs, IVIg), sign of HTN
  - Meningitis/encephalitis not common post-transplant
- Cardiopulmonary symptoms
  - High risk of CAD/CHF/AF in this population
  - Risk of DVT/PE in postoperative period
  - Use medical judgement re: need for ED referral

Aulagnon e al. Transplantation 98:806-816, 2014.

“My wound is falling apart, what should I do?”

- Patients who are having surgical issues (drains, drainage, dehiscence, etc) should speak with a surgeon
  - Call renal transplant PA (82729) or attending to contact surgical fellow

“My dose of medication doesn’t match what’s on the pill bottle”

- Medications are typically ordered for the patients a day or more before hospital discharge. The dose on the pill bottle may not match the dose that the patient is taking at the time of discharge.
- The patient should follow the dose on their discharge list of medications. If they are called and told to adjust one of their medications, they should take that dose, not the dose on the bottle or the discharge medication list.

“I’m returning a message my coordinator left but they didn’t say what it was about”

- If it’s still reasonably early, you can try calling their nephrologist.
- If it’s late at night, you can try seeing if there’s any documentation in EHR

“Help, I ran out of medications!”

- If it’s Sunday-Thursday – email the post-transplant coordinators. They will take care of the problem the next day.
- If it’s Friday-Saturday, speak with the on-call transplant attending or outpatient nephrologist to assist with prescribing the medication. Ideally, the patient should be able to identify a pharmacy that has the medication they need.

Other issues

- Calls from outside hospitals requesting transfer → contact transplant attending on call or refer to NYP Transfer Center (800-NYP-STAT)
- Something not covered in this talk → we'll figure it out ☺

Coordination of care

- Patients should not be told to come directly to the clinic in the morning to be seen (there may be no room available to see the patient, and the patient may have symptoms that put other patients at risk). The outpatient team will call the patient to arrange for appropriate follow up.
- You can/should call/text an attending with any questions.
- You should send an email in the morning for all issues that arise on call.
- Coordinator email addresses:
  - Posttransplantcoordinators@columbia.edu
  - pretransplantcoordinators@nyp.org
  - livingdonorcoordinators@nyp.org
- Attending group email
  - txnephrology@columbia.edu

Orientation to transplant rotation

Service structure (aka where do I fit in this picture?)

- Multidisciplinary team = crowded ~~room~~ WebEx
  - Transplant nephrology attending
  - Transplant surgery attending
  - Transplant nephrology fellow
  - Transplant surgery fellow (+/- Urology resident)
  - General surgery resident
  - Transplant PAs
  - Transplant pharmacist
  - General nephrology fellow(s) – internal and external
  - Others: PA students, pharmacy residents, medical students, visiting doctors

Types of patients on service

- Fresh transplant patients
  - Living and deceased donor kidney transplants
  - Pancreas transplants (SPK, PAK, PTA)
  - Living kidney donors
- Patients readmitted for transplant complications
  - Acute rejection
  - Surgical, infectious, medical (if in first year post-transplant)
  - Other (mainly first year post-transplant)
- Outfield patients
  - Admitted for non-transplant complications beyond the first year post-transplant

Your role on service

- Attend rounds
  - Morning – 9:00 WebEx – presentations typically done by transplant PA
  - Afternoon – 4:00 WebEx – review drug levels and discuss any new admissions
- Follow patients
  - Transplant fellow will assign you 1-3 patients to follow
  - Mix of fresh transplant patients, admissions for graft dysfunction, admissions for other post-transplant complications (infield and/or outfield)
- Note writing (new patients and follow ups)
  - Assessment/plan should reflect what has been discussed on rounds as well as your thoughts on what might be appropriate management
  - Your assessment should try to capture all of the issues relevant to transplant for that patient (donor, recipient, transplant characteristics)

What do I mean by “donor, recipient, transplant characteristics” (aka What do all these terms mean? Why do they matter?)

ESRD secondary to PKD

s/p LRRT 11/09/2004 – failed secondary to BK and chronic rejection

s/p DDRT 2/23/2018, thymo induction, terminal creatinine 3.1, KDPI 79%, EPTS 57%, PHS-IR, DCD, CIT 30h

CMV D+/R+, EBV D+/R+, HCV D+

DSA to A2 MFI 1,500

DGF

Admitted with 1B ACR + AMR

Other learning while on service

- Attend transplant evaluation clinic
  - Observe recipient/donor evaluations 1 afternoon/week while on service
- Attend selection conferences
  - Monday 8:00 (donor); Friday 8:00 (recipient)
- Case-based presentations
  - Assigned by attending
- Pathology rounds
  - Daily at 3:30 – inpatient and outpatient biopsies reviewed
- Non-transplant responsibilities while on service
  - Attend your CKD follow up clinic; do not go to transplant clinic
  - Do not schedule elective biopsies during rounds