CLINICAL GRAND ROUNDS

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THE CASE

- CC: weakness
- HPI:
  - 69M African American w/ ESRD secondary to FSGS s/p cadaveric renal transplant (1999), was on dialysis from 1991 to 1999, HTN, hemorrhoids presents from home due to weakness associated with dizziness, nonproductive cough, reduced oral intake and diarrhea with occasional hematochezia. Baseline creatinine 2.7-3.0 (since 2014) found to have sepsis due to pneumonia (consolidation on an ultrasound of the chest), AKI (creatinine 4.0), acute on chronic anemia. His AKI improved with fluid repletion (blood and IV fluids).
  - He stated that he had lost about 50 pounds over the past 4 years. This was associated with progressive weakness. He complained of chronic diarrhea of at least two years duration. He noticed blood on the toilet paper occasionally. He was told after his hemorrhoidectomy that he would have occasional bleeding. But he did state that at times it was like a “faucet” but would stop after a few minutes.
  - Takes his medications as prescribed. No sick contacts and no one is affected at home.
TRANSPLANT HISTORY

- 1999  cadaveric renal transplant at the Boston VA.
  - Induced with Daclizumab and steroids
  - Maintenance with tacrolimus, MMF 1 gram BID, prednisone

- 2003  Admitted for volume depletion secondary to diarrhea complicated by AKI
  - Negative workup included C.diff, fecal leukocytes, ova/parasite, cryptosporidium, microsporidia.
  - CMV titers, parvovirus titers
  - Colonoscopy/EGD with nonspecific colitis, gastritis. No evidence of viral infection

- 2004  MMF reduced to 750mg BID

- 2005  AKI in setting of diarrhea

- 2006  MMF stopped. Diarrhea improved.

- 2007  AKI, concern for rejection. Azathioprine started. Biopsy showed no rejection and no chronic allograft nephropathy

- 2012  diarrhea due to C.diff (recent antibiotic use). rest of workup negative.
OTHER HISTORY

- Surgical hx:
  - Cadaveric renal Tx 1999
  - Hemorrhoidectomy 2004
  - Hemorrhoid banding 1996
- Family hx: none
- Social hx: denies ETOH, illicit, quit tobacco 12 years ago, 20 pack years

- Medications
  - Azathioprine 75mg daily
  - Prednisone 5mg daily
  - Tacrolimus 0.5mg bedtime
  - Terazosin 5mg bedtime
  - Gabapentin 100mg TID
  - Sodium bicarbonate 1300mg BID
  - Cholecalciferol 1k IU daily
  - Cyanocobalamin 100mcg daily
  - Folic acid 1mg daily
Vitals: Tmax 101.9   HR 108-121   BP 114/61   MAPs 72-95

weight 88 lbs   Height 65 inches   BMI 14.6

General: elderly male, thin, temporal wasting, NAD, aaox3

Chest: clear to auscultation bilaterally

Cardiac: tachycardic, regular, s1 s2, no murmurs

Abdomen: soft, nt/nd, RLQ graft-nontender

Extremities: no edema
- BMP
  - Na
  - K
  - Cl
  - CO2
  - BUN
  - Creat
  - Glucose
  - Ca
  - Phos
  - Mg
- LFT
  - AST
  - ALT
  - Tbili
  - Alk phos
  - Tprot
  - Alb
- CBC
  - WBC
  - Hgb
  - Hct
  - Plt
  - MCV
  - RDW
- Urine studies
  - UA
    - pH
    - Small blood, RBC
    - Negative LE and nitrites
  - WBC
  - Pro
- Uprot
- Ucreat
- Infection workup
  - Blood cultures neg
  - Urine culture sensitive staph lugdunensis
MORE LABS

- Tacro 6.6
- Iron 8
- tibc 160
- ferritin 347
- B12 565
- CRP 11.8
- ESR 47

- Stool
  - Fecal leukocytes neg
  - Endomysial ab neg
  - Cdiff neg
  - Neg for campylobacter, salmonella, shigella, vibrio, Yersinia.
  - No ova, parasite, cyst
  - HIV neg
  - Stool virus neg (enterovirus and adenovirus)
HOSPITAL COURSE

- CMV DNA PCR  blood positive
- EBV DNA PCR 15k copies/mL
- Histo antigen urine neg
- parvo b19 DNA blood PCR neg
- Feces osm 349 couldn’t do electrolytes due to formed stool
- Serum fungitell inconclusive
- Mycology cx blood neg
- Parvo ab IGM 0.1
- Parvo ab IGG 4.6 (high)
DIARRHEA IN THE KIDNEY TRANSPLANT RECIPIENT

- What is it?
- Prevalence
- Causes
- Systematic way of managing it
- Risk of rejection with immunosuppressant dose adjustment
WHAT IS DIARRHEA?

- World Health Organization-approved definition of diarrhea:
  - three or more loose or liquids stools per day.
    - Acute diarrhea lasts <14 days
    - Persistent diarrhea >14 days to <1 month
    - Chronic diarrhea is >1 month
  - Unfortunately not everyone adheres to this.
TIMING OF DIARRHEA

- First month
  - Donor origin
  - GVHD
- 1-6 months
  - opportunistic infections
  - Viruses-adenovirus, astrovirus, rotavirus.
  - Bacteria-Cdiff
  - medication
- >6 months
  - community acquired pathogens
  - CMV colitis (delayed due to CMV prophylaxis)
  - medication

Goal was to evaluate the prevalence and management of GI complications in solid organ transplant recipients.

Epidemiologic multicenter study. 1788 total, 1132 renal transplants.

18% had pre-transplant GI disease. 53% (600 patients) of patients had post transplant GI complaints (of these patients, 50% (300) suffered from diarrhea)

- 71% got medical treatment (majority with gastric protectors)
- 47% had a change in their immunosuppressant regimen (mainly MMF)

No mention of improvement with above intervention.


Forty-one thousand patients. Follow up of 1-3 years

Three year cumulative incidence of 22%.

Eighteen percent of these were noninfectious with an unspecified cause. This diagnosis was associated with increased graft failure (HR 2.13), patient death (HR 2.04)

CAUSES

Infectious

- Bacteria (C.diff, shigella, salmonella, vibrio, E.coli, campylobacter, mycobacteria)
  - Bacterial overgrowth of the small intestine
- Viral (CMV, HSV, adenovirus, rotavirus, enterovirus, norovirus)
- Fungal/Parasitic

Non-Infectious

- Medications
  - Immunosuppressants
  - Non-immunosuppressants
    - Diuretics
    - Anti-HTN
    - PPI
    - DM meds
    - Antibiotics
    - others

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3716061/
http://www.antimicrobe.org/new/t12_dw.html
Cytomegalovirus is one of the most common infectious pathogens affecting solid organ transplant recipients. The most common target organ is the GI tract.

But other viruses are being increasingly recognized, including norovirus, rotavirus, and adenovirus.

Norovirus has been evaluated in a retrospective study in a single center. Eighty-seven patients were included and 46 of them had chronic diarrhea.

Twenty patients with unexplained diarrhea were screened for norovirus and sapovirus. Sixteen were positive.

Norovirus (gold standard is PCR of stool RNA or antigen)


DIDACT STUDY

- Prospective, multicenter. 108 patients
- Severe diarrhea (≥3 stools/day for ≥7 consecutive days) in renal transplant patients
- Stepwise approach to intervention

<table>
<thead>
<tr>
<th># patients</th>
<th>resolved</th>
<th>what worked</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>7</td>
<td>stop non-immunosuppressant</td>
</tr>
<tr>
<td>101</td>
<td>17</td>
<td>treat positive stool test</td>
</tr>
<tr>
<td>84</td>
<td>5</td>
<td>treat CMV</td>
</tr>
<tr>
<td>79</td>
<td>13</td>
<td>treat bacterial overgrowth</td>
</tr>
<tr>
<td>66</td>
<td>25</td>
<td>change immunosuppressants</td>
</tr>
<tr>
<td>41</td>
<td>13</td>
<td>colonoscopy then change immunosuppressants</td>
</tr>
<tr>
<td>28</td>
<td>11</td>
<td>anti-diarrhea meds, diet change, supplemental bacteria</td>
</tr>
<tr>
<td>17</td>
<td>12</td>
<td>re-evaluated (5 had +stool culture, 3 w/ +CMV, 4 w/ endoscopic lesions)</td>
</tr>
<tr>
<td>5</td>
<td>??</td>
<td>53/108 did not need immunosuppressant changes</td>
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IMMUNOSUPPRESSANT CHANGES AND REJECTION

- Focus on MMF because it is the most commonly adjusted medication.
Cohort of 721 kidney transplant recipients who were on MMF, cyclosporine and prednisone.

They evaluated the effect that MMF dose changes had on clinical outcomes in the first year-post transplant. Of the group with dose changes 21% had GI side effects (which included diarrhea), other side effects were hematological and infection related.

70% of patients had at least one dose change (75% had an initial reduction in dose). 71% of the dose changes occurred within the first 4 months.

At 1 year, they had a higher incidence of acute rejection (23.3% vs. 3.7%, p<0.001). There was also a significant decrease in graft survival over 3 years.

MMF DOSE REDUCTIONS

- MMF can lead to significant GI symptoms. Which triggers physicians to reduce/withdraw the medication.
  - USRDS data 1995-2001
  - 3600 patients with GI complications
  - Followed patients for 3 years starting from the first GI diagnosis based on medicare billing records
  - Primary outcome was graft failure (graft loss, return to dialysis, death)

- Sixty-nine percent had a GI diagnosis in the first year post-transplant. Median dose of MMF was 2g/day. ~50% of patients had a reduction or withdrawal of their MMF dose.

- MMF dose reduction >/=50% led to an increased risk of graft failure (HR=2.36). Average number of days with dose reduction was 85 days.

- MMF withdrawal (HR=2.72). Median days of discontinuation was 36 days.

MMF v. EC-MPS

- There are many trials (mostly open label) that have compared GI symptoms and quality of life of the two above.

- Randomized, multicenter, open label, 12 week study
- Renal transplant patients who were experiencing GI complications (diarrhea included) believed to be due to MMF.
- Fifty-four continued with MMF and 59 were switched to EC-MPS (equimolar doses)
- After 12 weeks there was significant difference in “GI quality of life” and HRQOL.
- Ortega F. et al., Gastrointestinal quality of life improvement of renal transplant recipients converted from mycophenolate mofetil to enteric-coated mycophenolate sodium drugs or agents: mycophenolate mofetil and enteric-coated mycophenolate sodium. Transplantation, 2011; 92 (4):426-32

- Single-center, open label randomized trial of MMF v. EC-MPS.
- One of the secondary aims was to assess GI side effects. The results were equivalent.
FIN