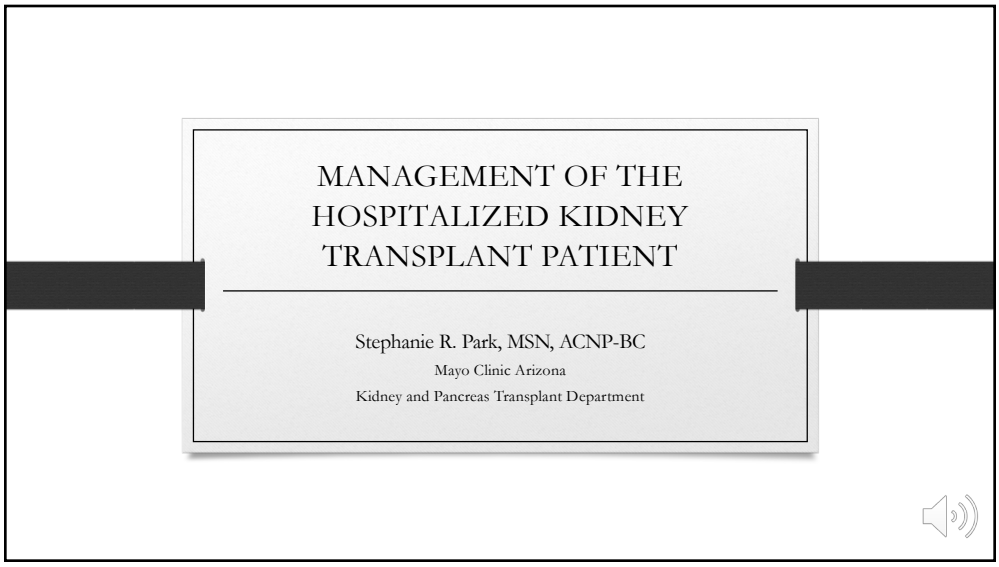
MANAGEMENT OF THE HOSPITALIZED KIDNEY TRANSPLANT PATIENT
Stephanie R. Park, MSN, ACNP-BC
Mayo Clinic Arizona
Kidney and Pancreas Transplant Department

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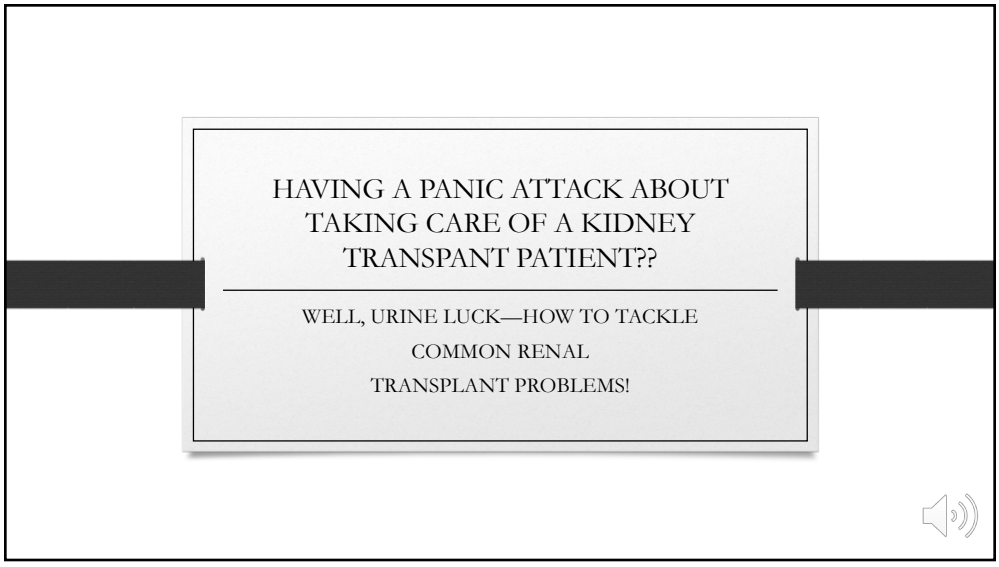

HAVING A PANIC ATTACK ABOUT TAKING CARE OF A KIDNEY TRANSPANT PATIENT??
WELL, URINE LUCK—HOW TO TACKLE COMMON RENAL TRANSPLANT PROBLEMS!

2

DISCLOSURES

- No relevant commercial relationships to disclose.
- Except…
  - My weakness for Diet Coke
  - My affinity for walls covered in shiplap (please call me, Joanna Gaines!)
  - My love for rescued pets

3

LEARNING OBJECTIVES

- Identify common drug regimens used in the setting of kidney transplantation
- Summarize steps to evaluate acute kidney injury of the renal allograft that may be different than the general population
- Identify approaches to treatment of urinary tract infections/pyelonephritis in the renal allograft
- Become familiar with common viral infection cytomegalovirus in the context of kidney transplant patients
- Evaluate and manage leukopenia in the setting of renal transplantation

4

TRANSPLANT IS A TREATMENT, NOT A CURE

- Kidney transplant recipients inevitably experience transplant-associated complications, often requiring hospitalization
  - Hospitalization rates 6 times higher than the general population (Jian et al., 2013)
- Hospital-based Physician Assistants and Nurse Practitioners will encounter kidney transplant patients and will be involved in the management of transplant-related complication

5

IMMUNOSUPPRESSION: OUR BEST FRIEND AND WORST ENEMY

- Goal of immunosuppression therapy: to reduce/block the alloimmune response to prevent rejection
  - Alloimmune response: Immune system response to antigens belonging to a member of the same species (non-self)
    - Transplant: Recipient T cells recognizing donor antigens as foreign
- Transplant teams are fighting the alloimmune response everyday!

6

IMMUNOSUPPRESSION: OUR BEST FRIEND AND WORST ENEMY

- Immunosuppression prevents rejection, but brings a myriad of complications
- Complications of immunosuppressive therapy:
  - Infection: bacterial, viral, fungal
  - Malignancy: skin cancer (most common), post-transplant lymphoproliferative disorder, and others
  - Drug-specific side-effects (see slides at end of presentation)

7

TRANSPLANT TEAM GOALS

- Balance amount of immunosuppression to prevent rejection while mitigating risks of complications
- Surveil for common transplant-related complications; treat early, when possible
- Treat aggressively in the outpatient setting
  - Avoid hospitalization, if possible
  - Despite our best efforts, hospitalization is sometimes necessary…

8

INPATIENT MANAGEMENT TEAMS

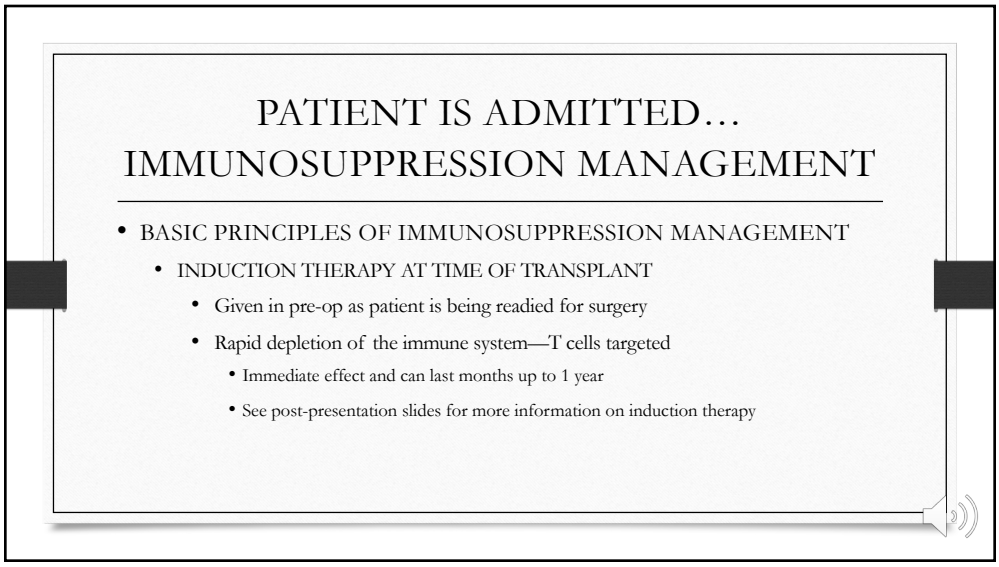
- EARLY POST-TRANSPLANT:
  - Attending team is the transplant team
  - Hospitalist/Internal Medicine teams typically not involved
    - In smaller hospitals (or those without a transplant program), this may not be the case
- LATE POST-TRANSPLANT:
  - Attending team is generally hospitalist/Internal Medicine Team
  - Transplant nephrologist (of general nephrologist) acts as consultant

9

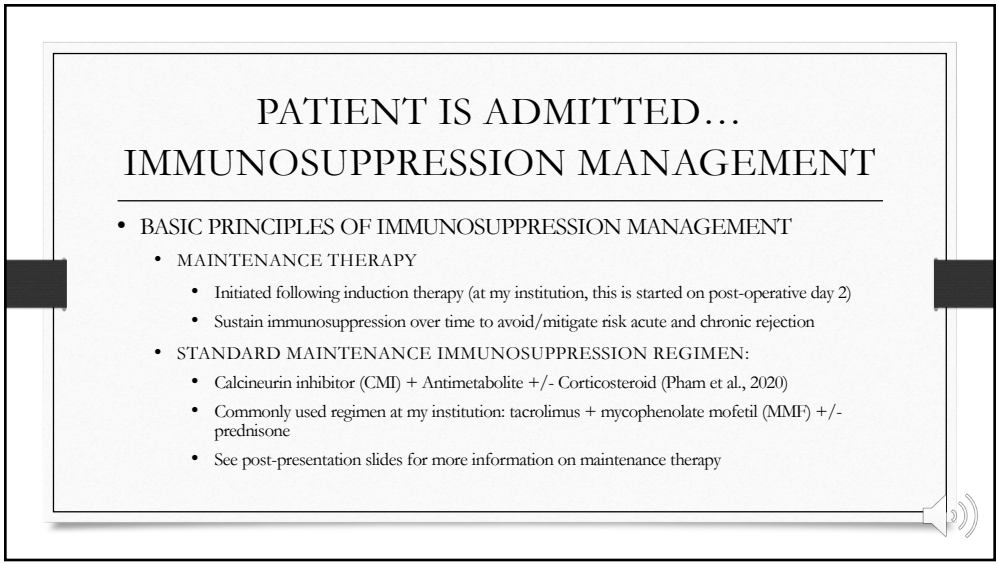
COMMON COMPLICATIONS REQUIRING HOSPITALIZATION

- EARLY POST-TRANSPLANT:
  - Surgical complications—Fever/infection, bleeding, renal artery or renal vein clotting, volume depletion)
  - Hyperglycemia—typically stemming from IV and oral steroid side-effect
  - Electrolyte imbalances—typically critical hyperkalemia
- LATE POST-TRANSPLANT >6 MONTHS:
  - Acute kidney injury (AKI)—Pre/intra/post-renal causes
  - Fever/bacterial infection—most commonly urinary tract infections (UTI) and bacteremia
  - Viral Infection—most commonly cytomegalovirus (CMV)

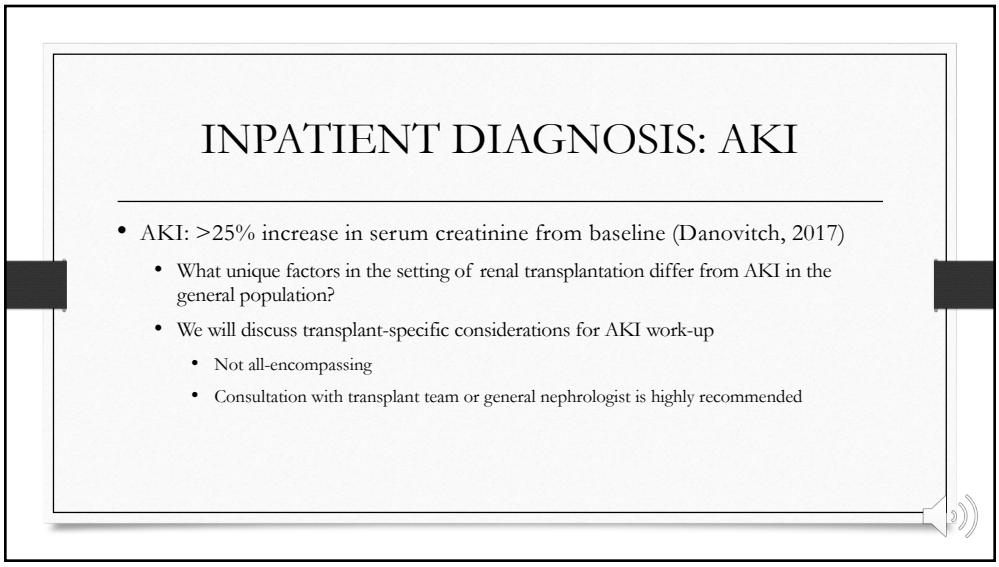
10


PATIENT IS ADMITTED…
IMMUNOSUPPRESSION MANAGEMENT
• BASIC PRINCIPLES OF IMMUNOSUPPRESSION MANAGEMENT
• INDUCTION THERAPY AT TIME OF TRANSPLANT
• Given in pre-op as patient is being readied for surgery
• Rapid depletion of the immune system—T cells targeted
• Immediate effect and can last months up to 1 year
• See post-presentation slides for more information on induction therapy

11


PATIENT IS ADMITTED…
IMMUNOSUPPRESSION MANAGEMENT
• BASIC PRINCIPLES OF IMMUNOSUPPRESSION MANAGEMENT
• MAINTENANCE THERAPY
• Initiated following induction therapy (at my institution, this is started on post-operative day 2)
• Sustain immunosuppression over time to avoid/mitigate risk acute and chronic rejection
• STANDARD MAINTENANCE IMMUNOSUPPRESSION REGIMEN:
• Calcineurin inhibitor (CMI) + Antimetabolite +/- Corticosteroid (Pham et al., 2020)
• Commonly used regimen at my institution: tacrolimus + mycophenolate mofetil (MMF) +/- prednisone
• See post-presentation slides for more information on maintenance therapy

12


INPATIENT DIAGNOSIS: AKI
• AKI: >25% increase in serum creatinine from baseline (Danovitch, 2017)
• What unique factors in the setting of renal transplantation differ from AKI in the general population?
• We will discuss transplant-specific considerations for AKI work-up
• Not all-encompassing
• Consultation with transplant team or general nephrologist is highly recommended

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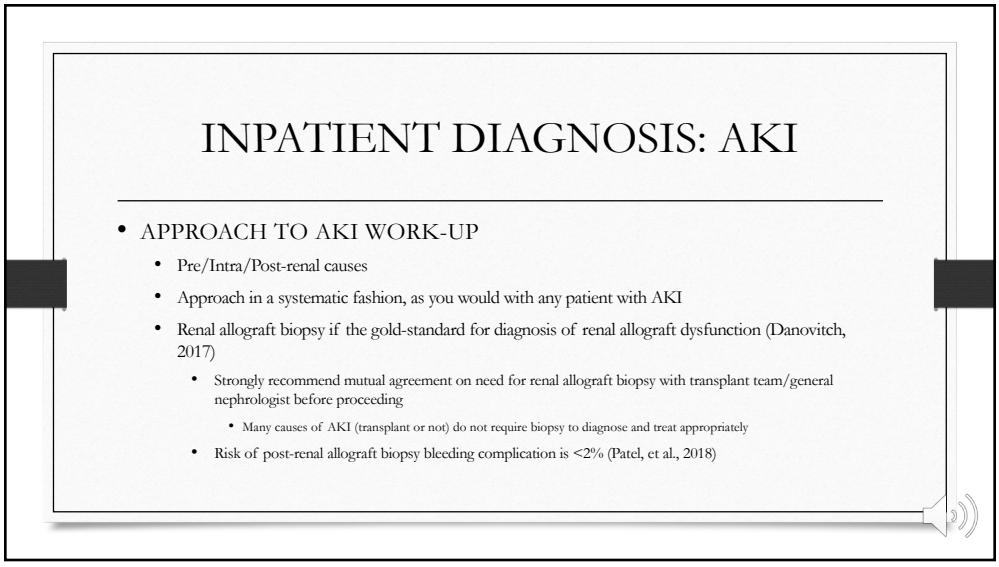
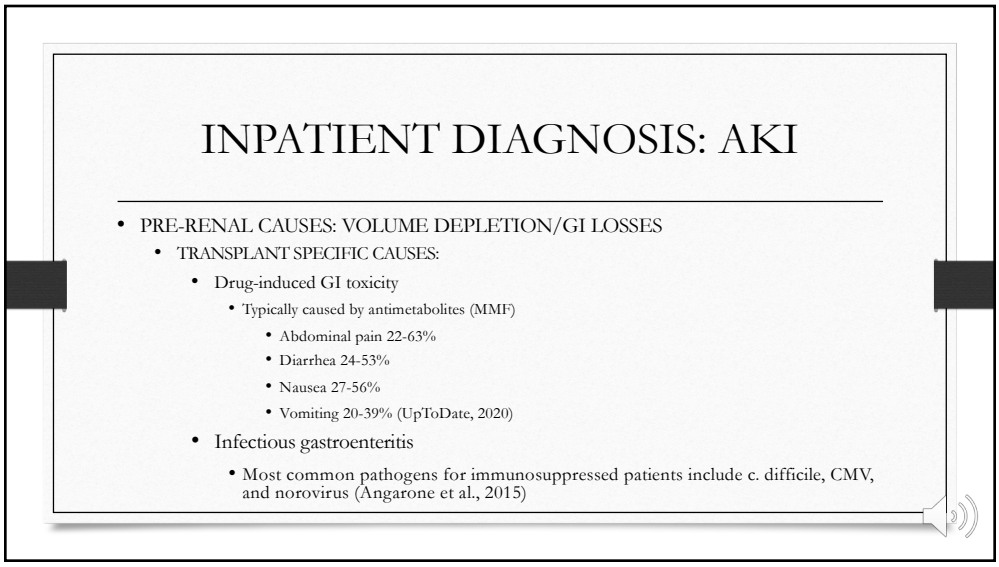
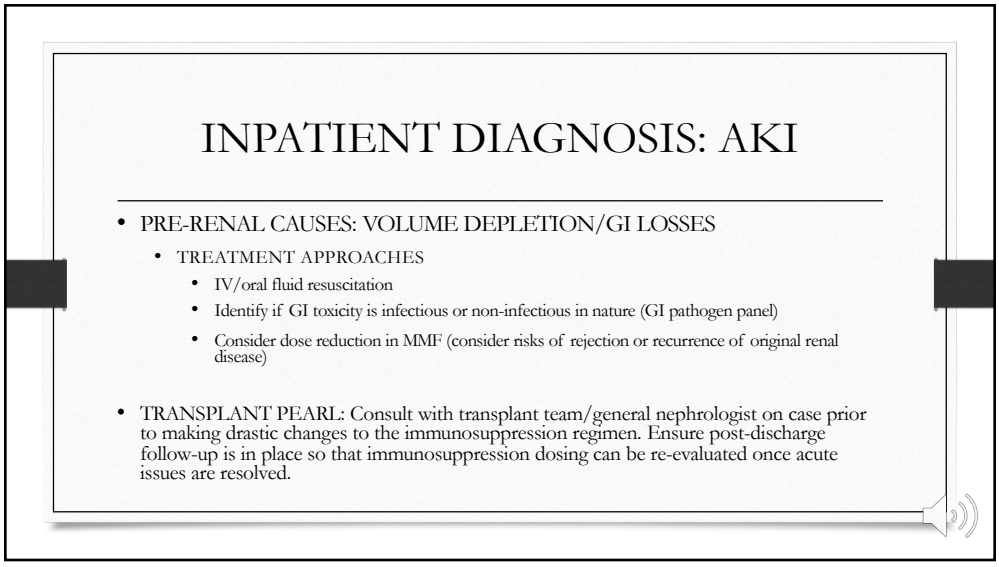

INPATIENT DIAGNOSIS: AKI
• APPROACH TO AKI WORK-UP
• Pre/Intra/Post-renal causes
• Approach in a systematic fashion, as you would with any patient with AKI
• Renal allograft biopsy if the gold-standard for diagnosis of renal allograft dysfunction (Danovitch, 2017)
• Strongly recommend mutual agreement on need for renal allograft biopsy with transplant team/general nephrologist before proceeding
• Many causes of AKI (transplant or not) do not require biopsy to diagnose and treat appropriately
• Risk of post-renal allograft biopsy bleeding complication is <2% (Patel, et al., 2018)

14


INPATIENT DIAGNOSIS: AKI
PRE-RENAL CAUSES: VOLUME DEPLETION/GI LOSSES
TRANSPLANT SPECIFIC CAUSES:
Drug-induced GI toxicity
Typically caused by antimetabolites (MMF)
Abdominal pain 22-63%
Diarrhea 24-53%
Nausea 27-56%
Vomiting 20-39% (UpToDate, 2020)
Infectious gastroenteritis
Most common pathogens for immunosuppressed patients include c. difficile, CMV, and norovirus (Angarone et al., 2015)

15


INPATIENT DIAGNOSIS: AKI
PRE-RENAL CAUSES: VOLUME DEPLETION/GI LOSSES
TREATMENT APPROACHES
IV/oral fluid resuscitation
Identify if GI toxicity is infectious or non-infectious in nature (GI pathogen panel)
Consider dose reduction in MMF (consider risks of rejection or recurrence of original renal disease)
TRANSPLANT PEARL: Consult with transplant team/general nephrologist on case prior to making drastic changes to the immunosuppression regimen. Ensure post-discharge follow-up is in place so that immunosuppression dosing can be re-evaluated once acute issues are resolved.

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INPATIENT DIAGNOSIS: AKI

- PRE-RENAL CAUSES: VOLUME DEPLETION/GI LOSSES
  - TREATMENT APPROACHES (CONTINUED)
    - INFECTION-INDUCED GI LOSSES
      - TRANSPLANT PEARL: Always rule out infection as cause of GI toxicity before assuming it is drug-induced.
        - GI infections are extremely common in transplant patients and approach to therapy is pathogen-specific. Guidance from Infectious Disease consultant is recommended.
      - TRANSPLANT PEARL: Probiotics safe to use in renal transplant patients
        - May improve GI symptoms in non-infectious diarrhea
        - Reconstitutes gut flora while undergoing therapy for infectious etiologies
        - Avoid probiotics with saccharomyces (yeast) due to risk of fungemia in immunocompromised host (Muñoz et al., 2005)
        - Lactobacillus, acidophilus, and Bifidobacterium infantis OK to use

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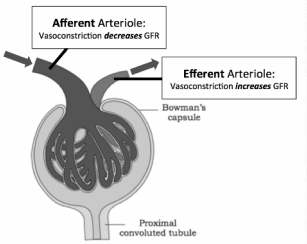
INPATIENT DIAGNOSIS: AKI

- PRE-RENAL CAUSES: CALCINEURIN INHIBITOR (CNI) TOXICITY
  - TACROLIMUS AND CYCLOSPORINE
    - Drug causes afferent arteriole vasoconstriction→worsens with increasing drug levels
    - Reduction in afferent arteriole blood flow→reduction in GFR→elevation in serum creatinine
    - Elevation in serum CNI levels increase risk of AKI.
    - Drug dosing titrated to a narrow therapeutic index
      - Tacrolimus 12 hour trough goal: 6-8 ng/mL
      - Cyclosporine 12 hour trough goal: 100-200 ng/mL
      - **These drug goals are institution-specific and may vary



Microvascular modulation of glomerular filtration rate (GFR)

(FARKAS, 2016)

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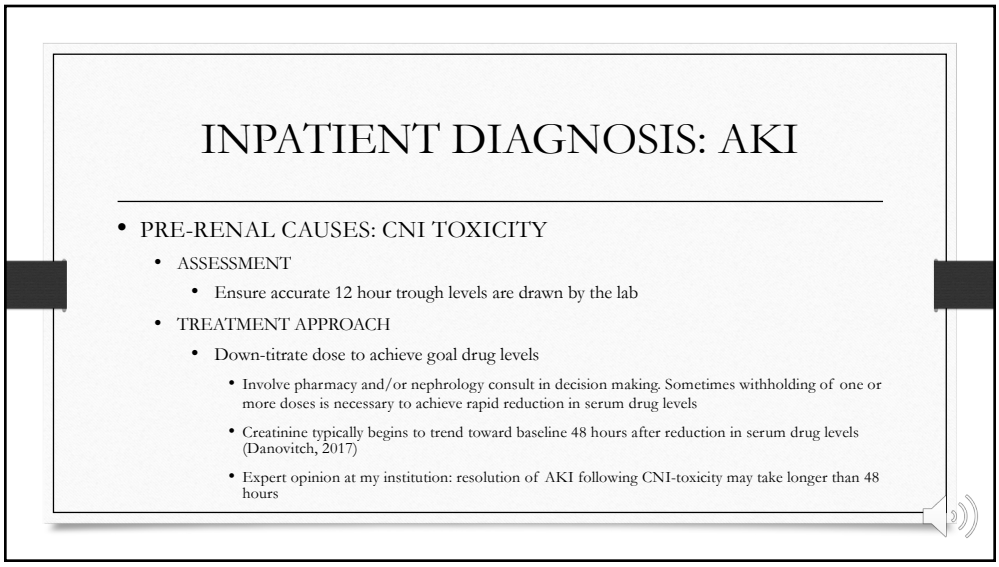
INPATIENT DIAGNOSIS: AKI
PRE-RENAL CAUSES: CNI TOXICITY
ASSESSMENT
Ensure accurate 12 hour trough levels are drawn by the lab
TREATMENT APPROACH
Down-titrate dose to achieve goal drug levels
Involve pharmacy and/or nephrology consult in decision making. Sometimes withholding of one or more doses is necessary to achieve rapid reduction in serum drug levels
Creatinine typically begins to trend toward baseline 48 hours after reduction in serum drug levels (Danovitch, 2017)
Expert opinion at my institution: resolution of AKI following CNI-toxicity may take longer than 48 hours

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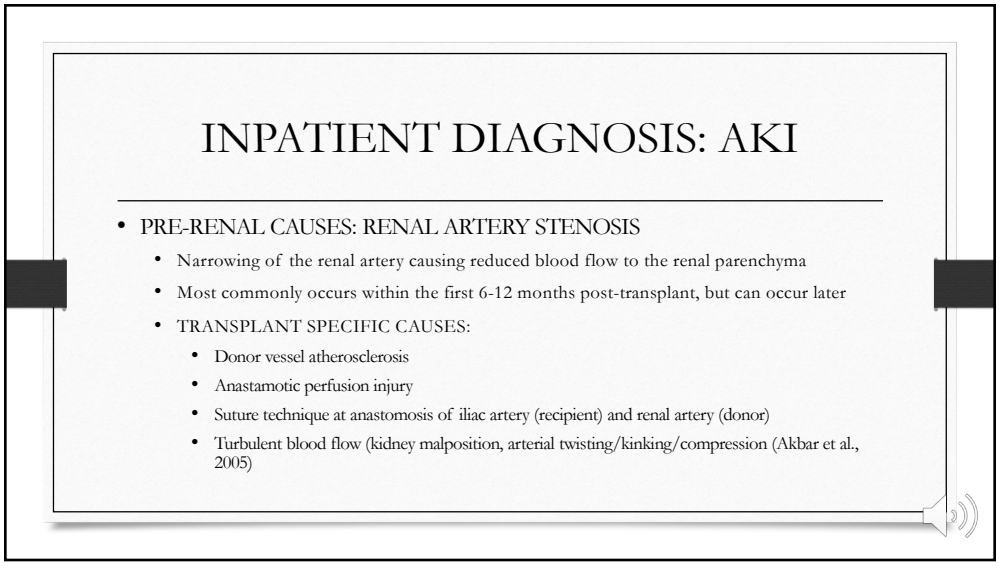
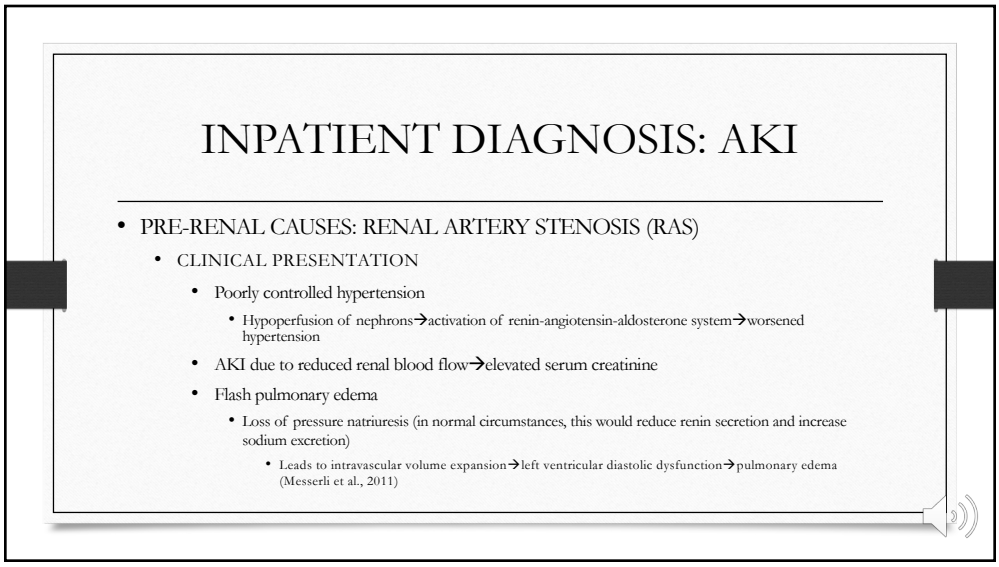

INPATIENT DIAGNOSIS: AKI
PRE-RENAL CAUSES: RENAL ARTERY STENOSIS
Narrowing of the renal artery causing reduced blood flow to the renal parenchyma
Most commonly occurs within the first 6-12 months post-transplant, but can occur later
TRANSPLANT SPECIFIC CAUSES:
Donor vessel atherosclerosis
Anastamotic perfusion injury
Suture technique at anastomosis of iliac artery (recipient) and renal artery (donor)
Turbulent blood flow (kidney malposition, arterial twisting/kinking/compression (Akbar et al., 2005)

20


INPATIENT DIAGNOSIS: AKI
• PRE-RENAL CAUSES: RENAL ARTERY STENOSIS (RAS)
• CLINICAL PRESENTATION
• Poorly controlled hypertension
• Hypoperfusion of nephrons→activation of renin-angiotensin-aldosterone system→worsened hypertension
• AKI due to reduced renal blood flow→elevated serum creatinine
• Flash pulmonary edema
• Loss of pressure natriuresis (in normal circumstances, this would reduce renin secretion and increase sodium excretion)
• Leads to intravascular volume expansion→left ventricular diastolic dysfunction→pulmonary edema (Messerli et al., 2011)

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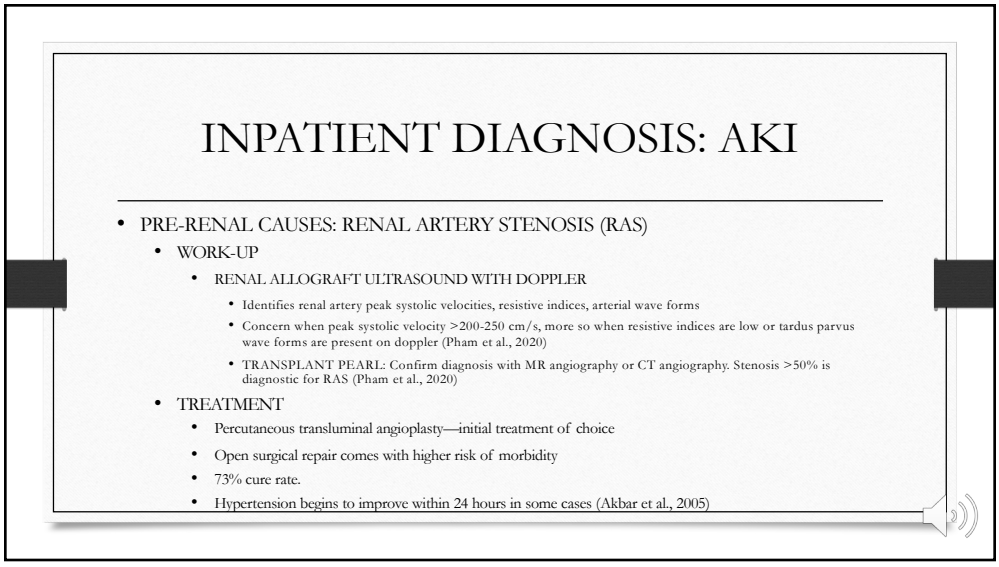
INPATIENT DIAGNOSIS: AKI
• PRE-RENAL CAUSES: RENAL ARTERY STENOSIS (RAS)
• WORK-UP
• RENAL ALLOGRAFT ULTRASOUND WITH DOPPLER
• Identifies renal artery peak systolic velocities, resistive indices, arterial wave forms
• Concern when peak systolic velocity >200-250 cm/s, more so when resistive indices are low or tardus parvus wave forms are present on doppler (Pham et al., 2020)
• TRANSPLANT PEARL: Confirm diagnosis with MR angiography or CT angiography. Stenosis >50% is diagnostic for RAS (Pham et al., 2020)
• TREATMENT
• Percutaneous transluminal angioplasty—initial treatment of choice
• Open surgical repair comes with higher risk of morbidity
• 73% cure rate.
• Hypertension begins to improve within 24 hours in some cases (Akbar et al., 2005)

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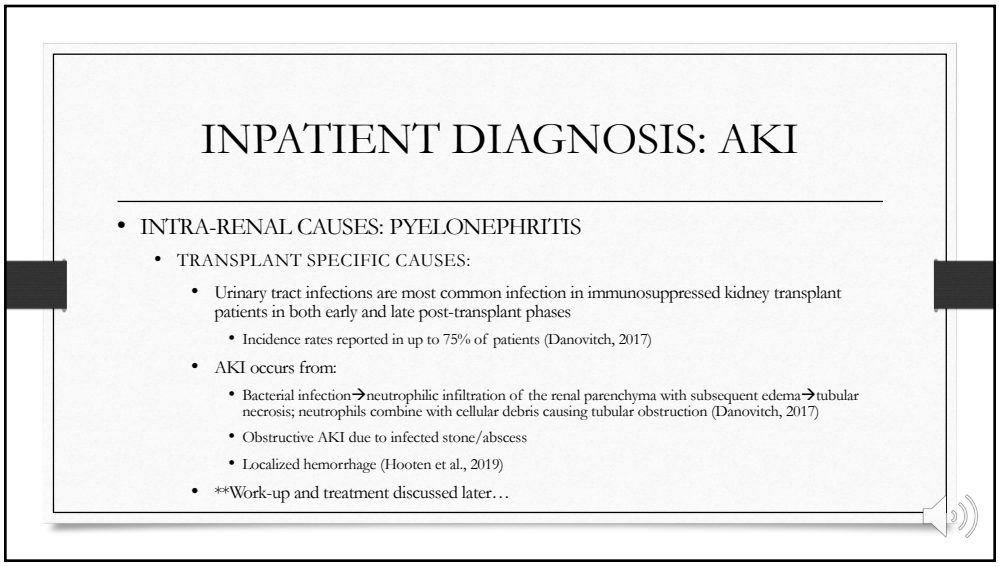
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: PYELONEPHRITIS
• TRANSPLANT SPECIFIC CAUSES:
• Urinary tract infections are most common infection in immunosuppressed kidney transplant patients in both early and late post-transplant phases
• Incidence rates reported in up to 75% of patients (Danovitch, 2017)
• AKI occurs from:
• Bacterial infection→neutrophilic infiltration of the renal parenchyma with subsequent edema→tubular necrosis; neutrophils combine with cellular debris causing tubular obstruction (Danovitch, 2017)
• Obstructive AKI due to infected stone/abscess
• Localized hemorrhage (Hooten et al., 2019)
• **Work-up and treatment discussed later…

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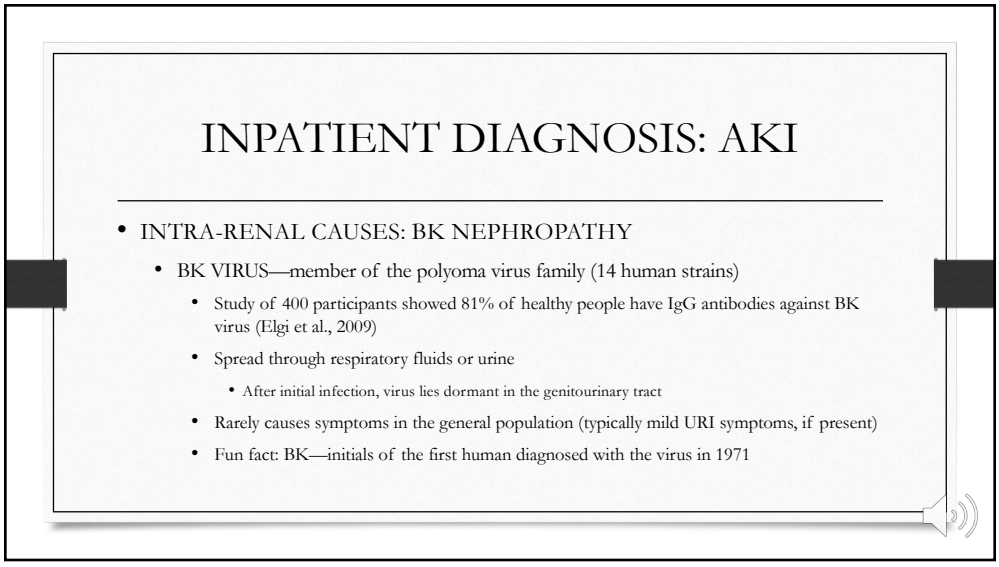
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: BK NEPHROPATHY
• BK VIRUS—member of the polyoma virus family (14 human strains)
• Study of 400 participants showed 81% of healthy people have IgG antibodies against BK virus (Elgi et al., 2009)
• Spread through respiratory fluids or urine
• After initial infection, virus lies dormant in the genitourinary tract
• Rarely causes symptoms in the general population (typically mild URI symptoms, if present)
• Fun fact: BK—initials of the first human diagnosed with the virus in 1971

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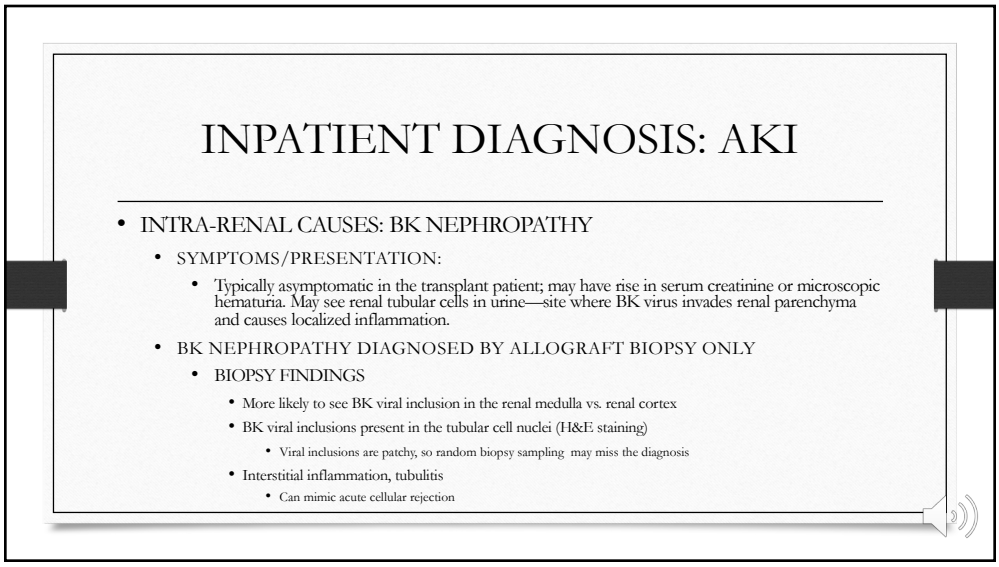
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: BK NEPHROPATHY
• SYMPTOMS/PRESENTATION:
• Typically asymptomatic in the transplant patient; may have rise in serum creatinine or microscopic hematuria. May see renal tubular cells in urine—site where BK virus invades renal parenchyma and causes localized inflammation.
• BK NEPHROPATHY DIAGNOSED BY ALLOGRAFT BIOPSY ONLY
• BIOPSY FINDINGS
• More likely to see BK viral inclusion in the renal medulla vs. renal cortex
• BK viral inclusions present in the tubular cell nuclei (H&E staining)
• Viral inclusions are patchy, so random biopsy sampling may miss the diagnosis
• Interstitial inflammation, tubulitis
• Can mimic acute cellular rejection

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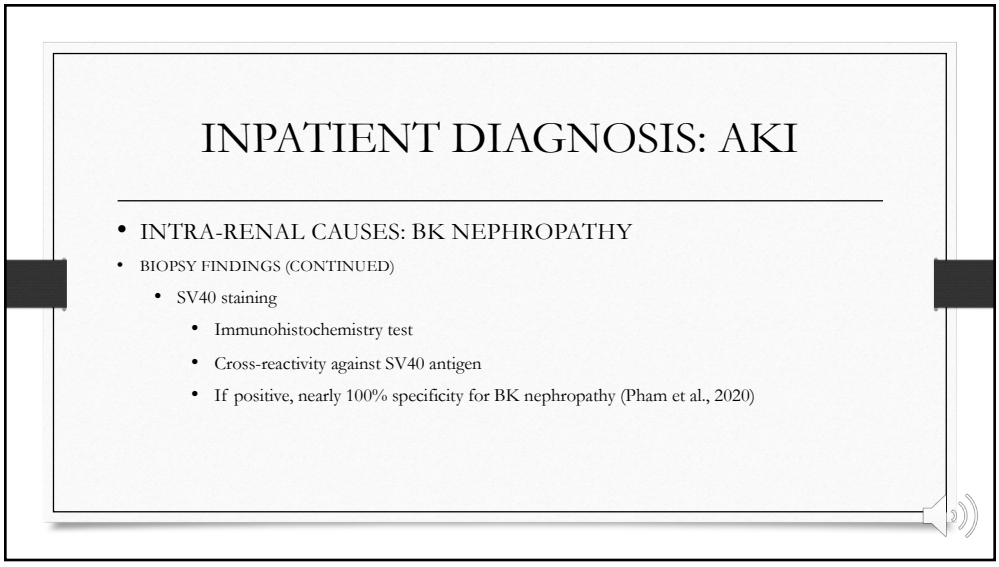
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: BK NEPHROPATHY
• BIOPSY FINDINGS (CONTINUED)
• SV40 staining
• Immunohistochemistry test
• Cross-reactivity against SV40 antigen
• If positive, nearly 100% specificity for BK nephropathy (Pham et al., 2020)

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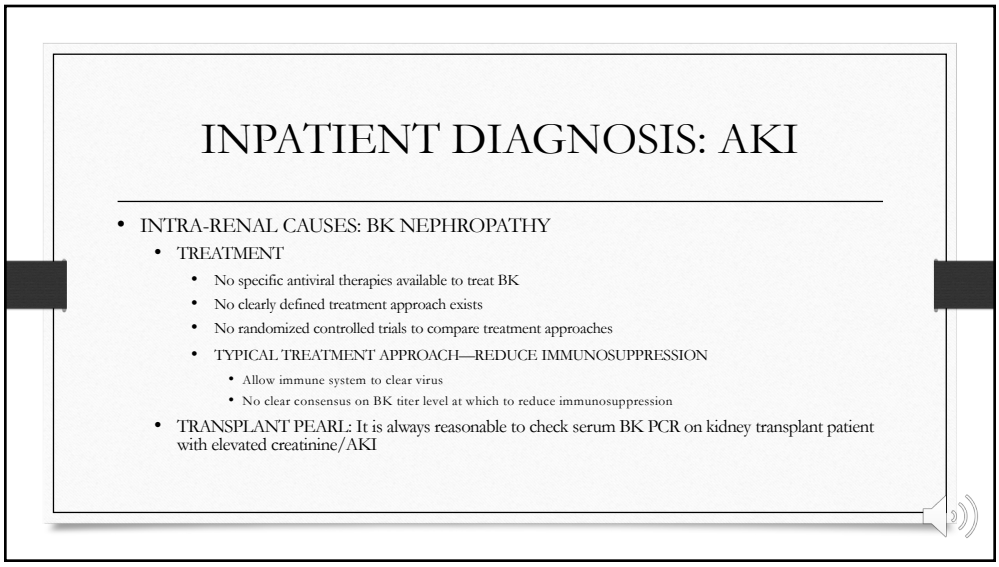
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: BK NEPHROPATHY
• TREATMENT
• No specific antiviral therapies available to treat BK
• No clearly defined treatment approach exists
• No randomized controlled trials to compare treatment approaches
• TYPICAL TREATMENT APPROACH—REDUCE IMMUNOSUPPRESSION
• Allow immune system to clear virus
• No clear consensus on BK titer level at which to reduce immunosuppression
• TRANSPLANT PEARL: It is always reasonable to check serum BK PCR on kidney transplant patient with elevated creatinine/AKI

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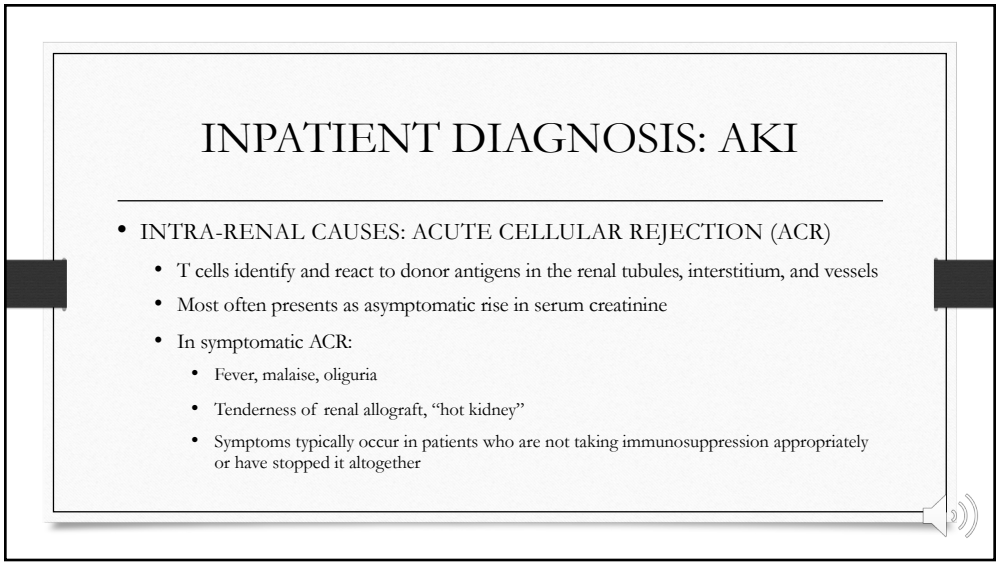
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: ACUTE CELLULAR REJECTION (ACR)
• T cells identify and react to donor antigens in the renal tubules, interstitium, and vessels
• Most often presents as asymptomatic rise in serum creatinine
• In symptomatic ACR:
• Fever, malaise, oliguria
• Tenderness of renal allograft, "hot kidney"
• Symptoms typically occur in patients who are not taking immunosuppression appropriately or have stopped it altogether

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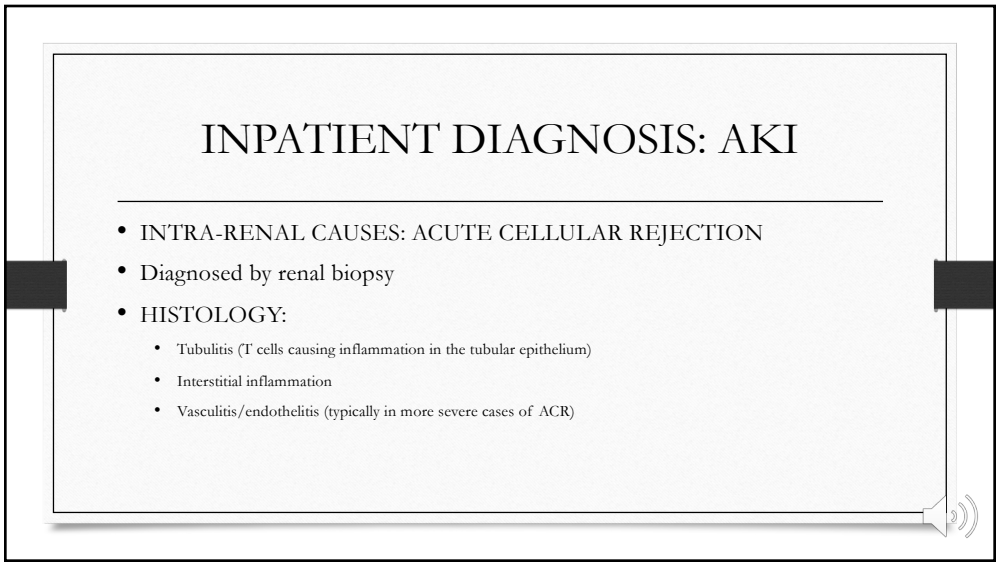
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: ACUTE CELLULAR REJECTION
• Diagnosed by renal biopsy
• HISTOLOGY:
• Tubulitis (T cells causing inflammation in the tubular epithelium)
• Interstitial inflammation
• Vasculitis/endothelitis (typically in more severe cases of ACR)

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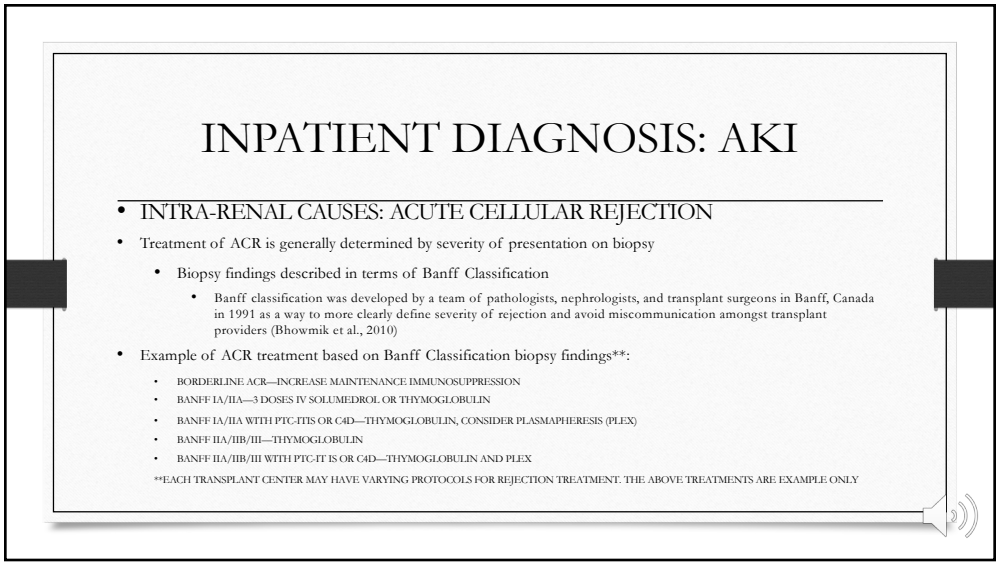
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: ACUTE CELLULAR REJECTION
• Treatment of ACR is generally determined by severity of presentation on biopsy
• Biopsy findings described in terms of Banff Classification
• Banff classification was developed by a team of pathologists, nephrologists, and transplant surgeons in Banff, Canada in 1991 as a way to more clearly define severity of rejection and avoid miscommunication amongst transplant providers (Bhowmik et al., 2010)
• Example of ACR treatment based on Banff Classification biopsy findings**:
• BORDERLINE ACR—INCREASE MAINTENANCE IMMUNOSUPPRESSION
• BANFF IA/IIA—3 DOSES IV SOLUMEDROL OR THYMOGLOBULIN
• BANFF IA/IIA WITH PTC-ITIS OR C4D—THYMOGLOBULIN, CONSIDER PLASMAPHERESIS (PLEX)
• BANFF IIA/IIB/III—THYMOGLOBULIN
• BANFF IIA/IIB/III WITH PTC-IT IS OR C4D—THYMOGLOBULIN AND PLEX
**EACH TRANSPLANT CENTER MAY HAVE VARYING PROTOCOLS FOR REJECTION TREATMENT. THE ABOVE TREATMENTS ARE EXAMPLE ONLY

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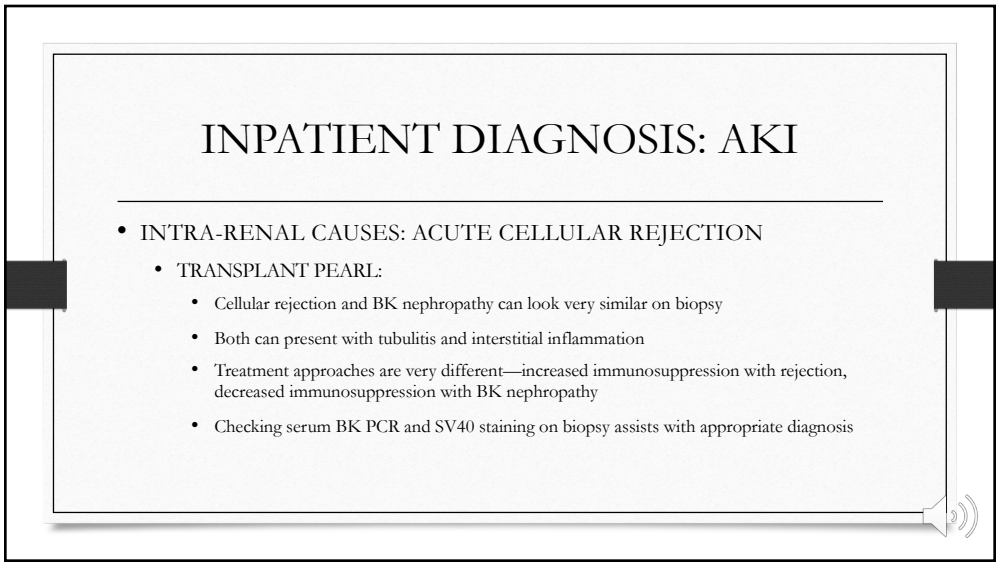
INPATIENT DIAGNOSIS: AKI
• INTRA-RENAL CAUSES: ACUTE CELLULAR REJECTION
• TRANSPLANT PEARL:
• Cellular rejection and BK nephropathy can look very similar on biopsy
• Both can present with tubulitis and interstitial inflammation
• Treatment approaches are very different—increased immunosuppression with rejection, decreased immunosuppression with BK nephropathy
• Checking serum BK PCR and SV40 staining on biopsy assists with appropriate diagnosis

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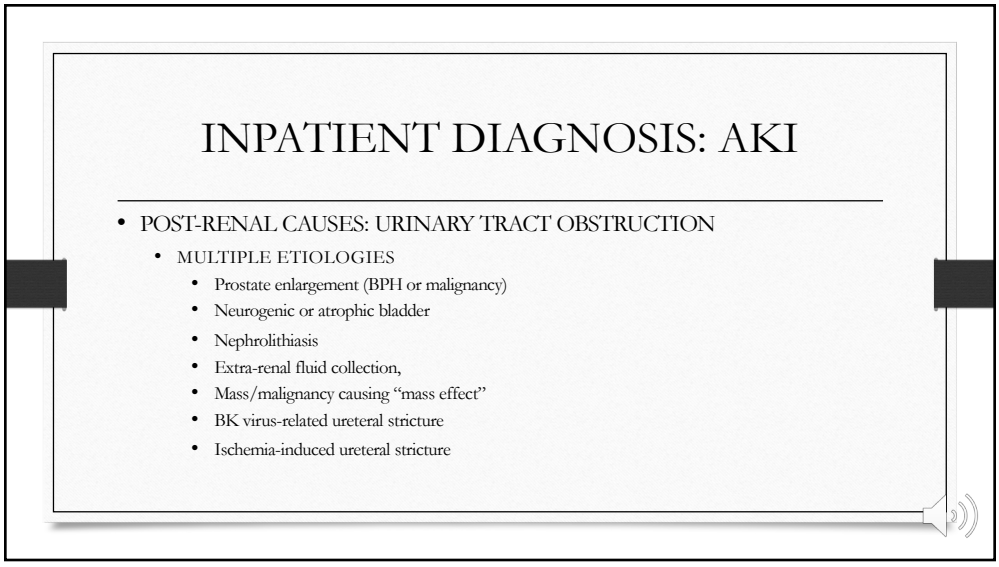
INPATIENT DIAGNOSIS: AKI
• POST-RENAL CAUSES: URINARY TRACT OBSTRUCTION
• MULTIPLE ETIOLOGIES
• Prostate enlargement (BPH or malignancy)
• Neurogenic or atrophic bladder
• Nephrolithiasis
• Extra-renal fluid collection,
• Mass/malignancy causing "mass effect"
• BK virus-related ureteral stricture
• Ischemia-induced ureteral stricture

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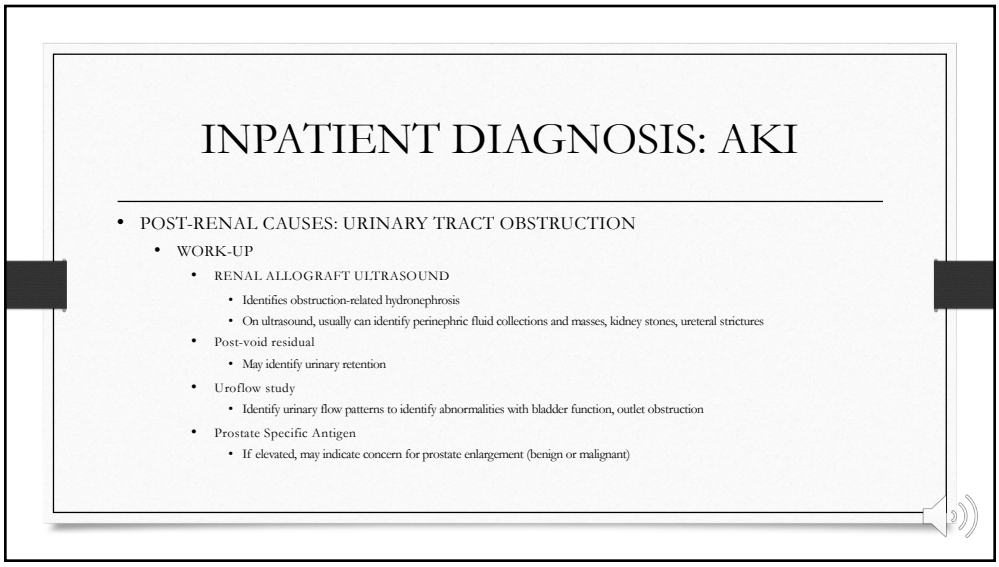
INPATIENT DIAGNOSIS: AKI
• POST-RENAL CAUSES: URINARY TRACT OBSTRUCTION
• WORK-UP
• RENAL ALLOGRAFT ULTRASOUND
• Identifies obstruction-related hydronephrosis
• On ultrasound, usually can identify perinephric fluid collections and masses, kidney stones, ureteral strictures
• Post-void residual
• May identify urinary retention
• Uroflow study
• Identify urinary flow patterns to identify abnormalities with bladder function, outlet obstruction
• Prostate Specific Antigen
• If elevated, may indicate concern for prostate enlargement (benign or malignant)

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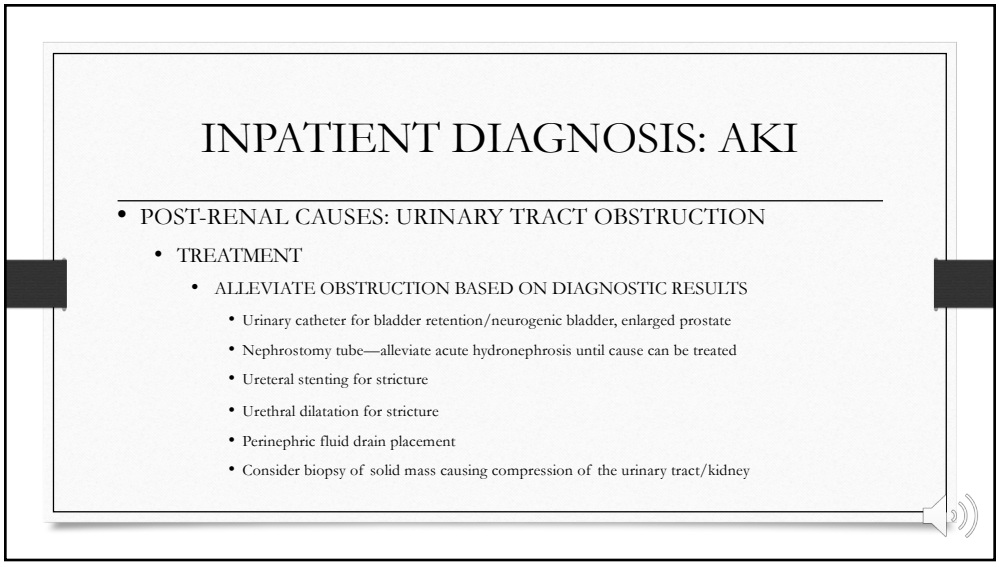
INPATIENT DIAGNOSIS: AKI
• POST-RENAL CAUSES: URINARY TRACT OBSTRUCTION
• TREATMENT
• ALLEVIATE OBSTRUCTION BASED ON DIAGNOSTIC RESULTS
• Urinary catheter for bladder retention/neurogenic bladder, enlarged prostate
• Nephrostomy tube—alleviate acute hydronephrosis until cause can be treated
• Ureteral stenting for stricture
• Urethral dilatation for stricture
• Perinephric fluid drain placement
• Consider biopsy of solid mass causing compression of the urinary tract/kidney

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INPATIENT DIAGNOSIS: AKI

- POST-RENAL CAUSES: URINARY TRACT OBSTRUCTION
  - TRANSPLANT PEARLS:
    - BK virus infection can cause ureteral stenosis
    - Bladder cancer incidence is higher in transplant population (mass may cause outlet obstruction)
    - Transplant ureter at high risk of ischemia→stricture can occur from ischemia
    - Transplant ureter can be re-implanted into the bladder after removal of strictured portion (typically, a robotic approach)

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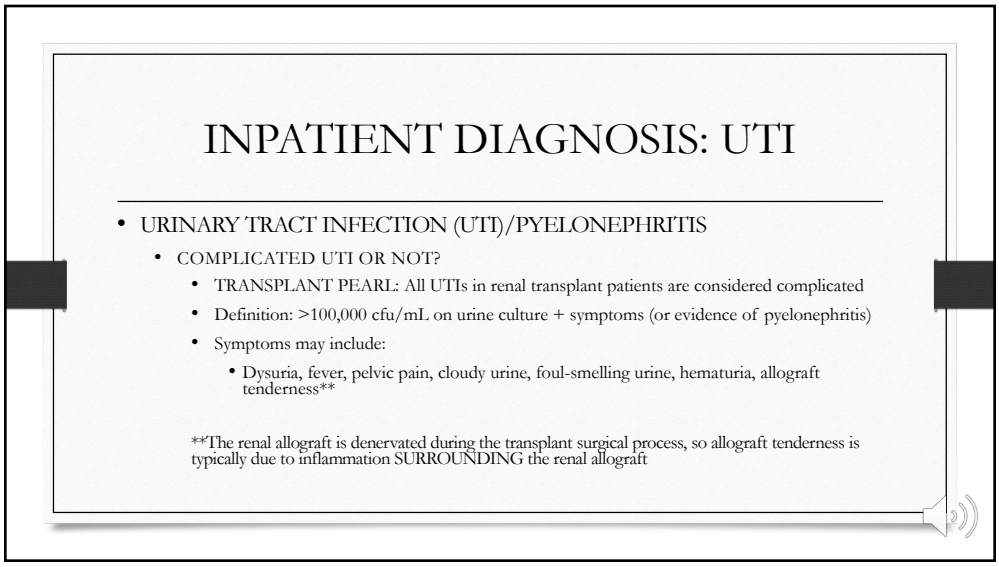
INPATIENT DIAGNOSIS: UTI

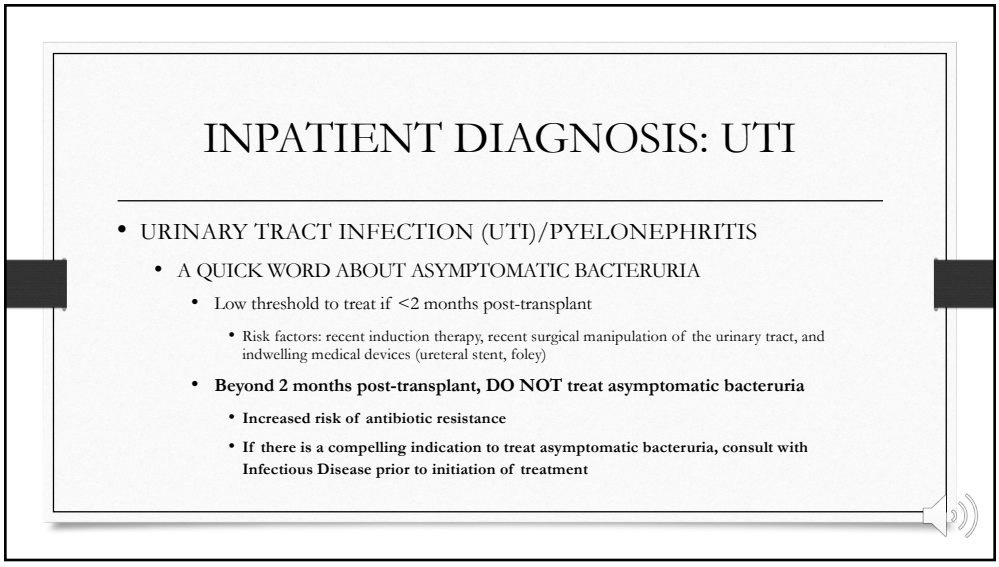
- URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
  - INCIDENCE
    - 17% within the first 6 months
    - 60% (women) and 47% (men) by year three**
    - E. coli is the most common bacterial pathogen (Karuthu et al., 2012)

**Some studies indicate UTI incidence is as high as 75% in long-term post-kidney transplant patients (Danovitch, 2017)

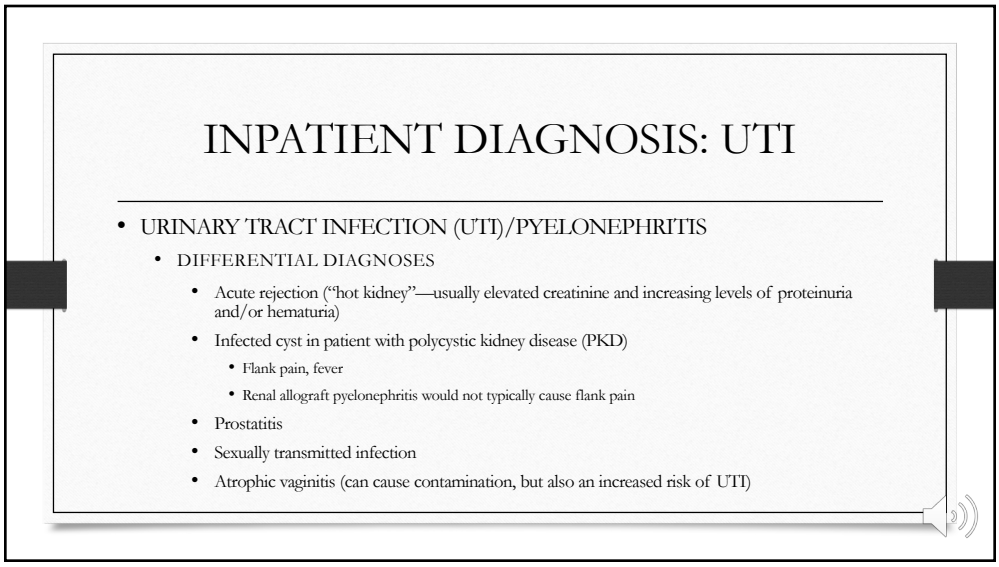
36


INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• COMPLICATED UTI OR NOT?
• TRANSPLANT PEARL: All UTIs in renal transplant patients are considered complicated
• Definition: >100,000 cfu/mL on urine culture + symptoms (or evidence of pyelonephritis)
• Symptoms may include:
• Dysuria, fever, pelvic pain, cloudy urine, foul-smelling urine, hematuria, allograft tenderness**
**The renal allograft is denervated during the transplant surgical process, so allograft tenderness is typically due to inflammation SURROUNDING the renal allograft

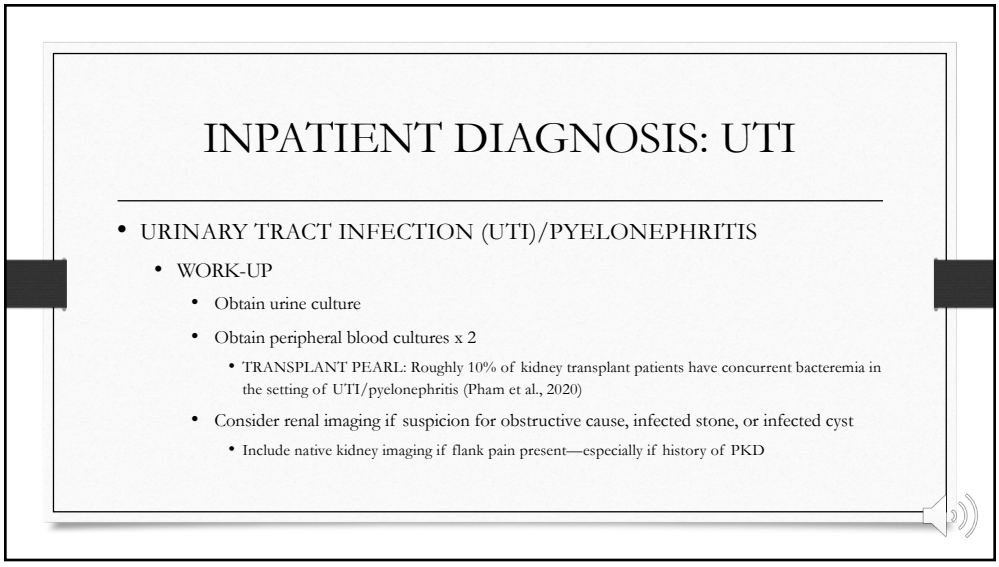
37


INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• A QUICK WORD ABOUT ASYMPTOMATIC BACTERURIA
• Low threshold to treat if <2 months post-transplant
• Risk factors: recent induction therapy, recent surgical manipulation of the urinary tract, and indwelling medical devices (ureteral stent, foley)
• Beyond 2 months post-transplant, DO NOT treat asymptomatic bacteruria
• Increased risk of antibiotic resistance
• If there is a compelling indication to treat asymptomatic bacteruria, consult with Infectious Disease prior to initiation of treatment

38


INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• DIFFERENTIAL DIAGNOSES
• Acute rejection ("hot kidney"—usually elevated creatinine and increasing levels of proteinuria and/or hematuria)
• Infected cyst in patient with polycystic kidney disease (PKD)
• Flank pain, fever
• Renal allograft pyelonephritis would not typically cause flank pain
• Prostatitis
• Sexually transmitted infection
• Atrophic vaginitis (can cause contamination, but also an increased risk of UTI)

39


INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• WORK-UP
• Obtain urine culture
• Obtain peripheral blood cultures x 2
• TRANSPLANT PEARL: Roughly 10% of kidney transplant patients have concurrent bacteremia in the setting of UTI/pyelonephritis (Pham et al., 2020)
• Consider renal imaging if suspicion for obstructive cause, infected stone, or infected cyst
• Include native kidney imaging if flank pain present—especially if history of PKD

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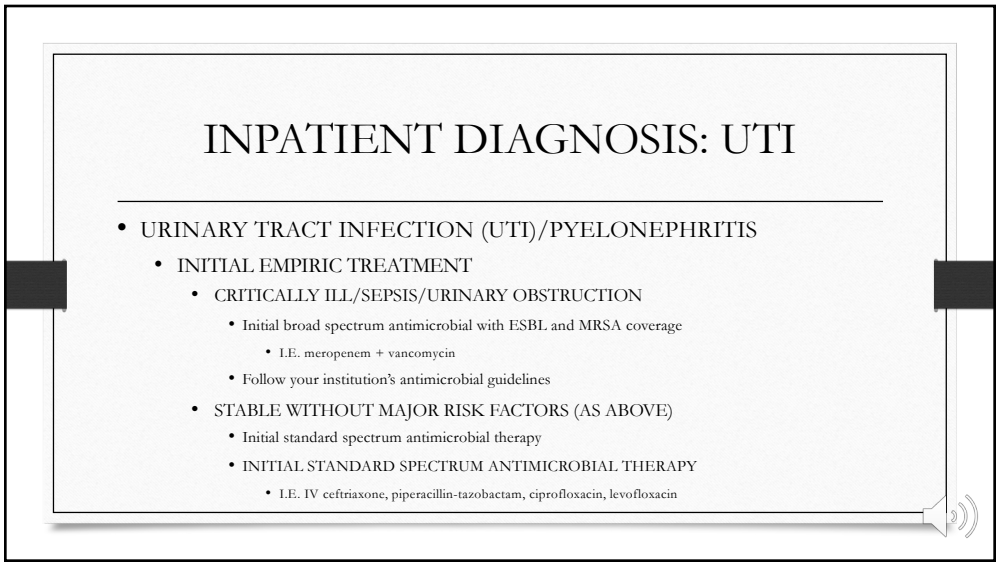
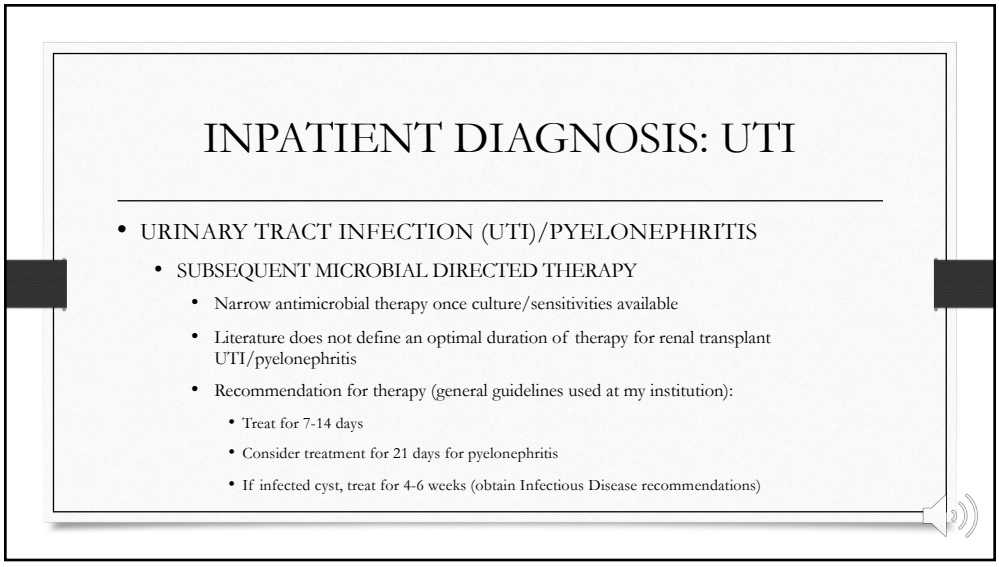

INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• INITIAL EMPIRIC TREATMENT
• CRITICALLY ILL/SEPSIS/URINARY OBSTRUCTION
• Initial broad spectrum antimicrobial with ESBL and MRSA coverage
• I.E. meropenem + vancomycin
• Follow your institution's antimicrobial guidelines
• STABLE WITHOUT MAJOR RISK FACTORS (AS ABOVE)
• Initial standard spectrum antimicrobial therapy
• INITIAL STANDARD SPECTRUM ANTIMICROBIAL THERAPY
• I.E. IV ceftriaxone, piperacillin-tazobactam, ciprofloxacin, levofloxacin

41


INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• SUBSEQUENT MICROBIAL DIRECTED THERAPY
• Narrow antimicrobial therapy once culture/sensitivities available
• Literature does not define an optimal duration of therapy for renal transplant UTI/pyelonephritis
• Recommendation for therapy (general guidelines used at my institution):
• Treat for 7-14 days
• Consider treatment for 21 days for pyelonephritis
• If infected cyst, treat for 4-6 weeks (obtain Infectious Disease recommendations)

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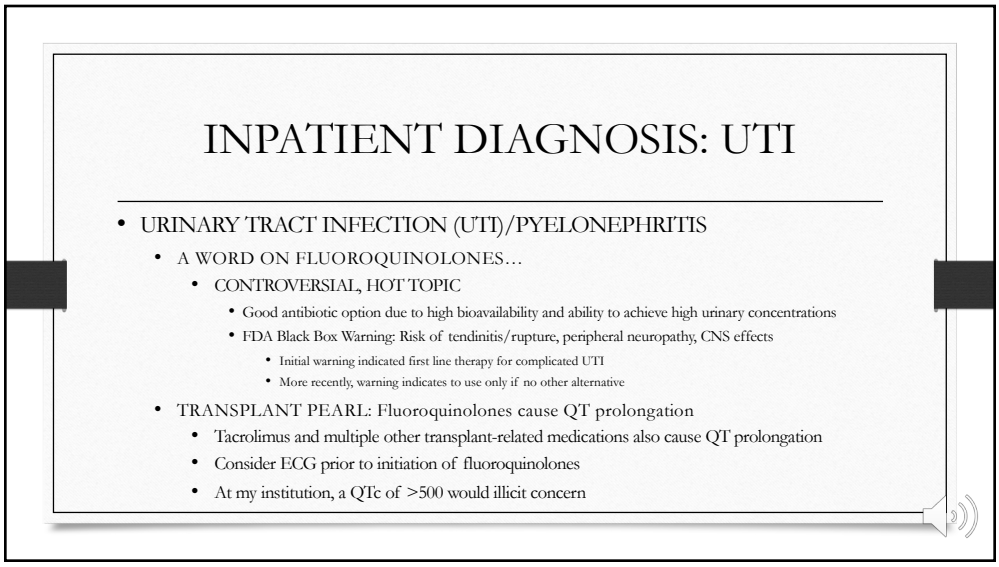
INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• A WORD ON FLUOROQUINOLONES…
• CONTROVERSIAL, HOT TOPIC
• Good antibiotic option due to high bioavailability and ability to achieve high urinary concentrations
• FDA Black Box Warning: Risk of tendinitis/rupture, peripheral neuropathy, CNS effects
• Initial warning indicated first line therapy for complicated UTI
• More recently, warning indicates to use only if no other alternative
• TRANSPLANT PEARL: Fluoroquinolones cause QT prolongation
• Tacrolimus and multiple other transplant-related medications also cause QT prolongation
• Consider ECG prior to initiation of fluoroquinolones
• At my institution, a QTc of >500 would illicit concern

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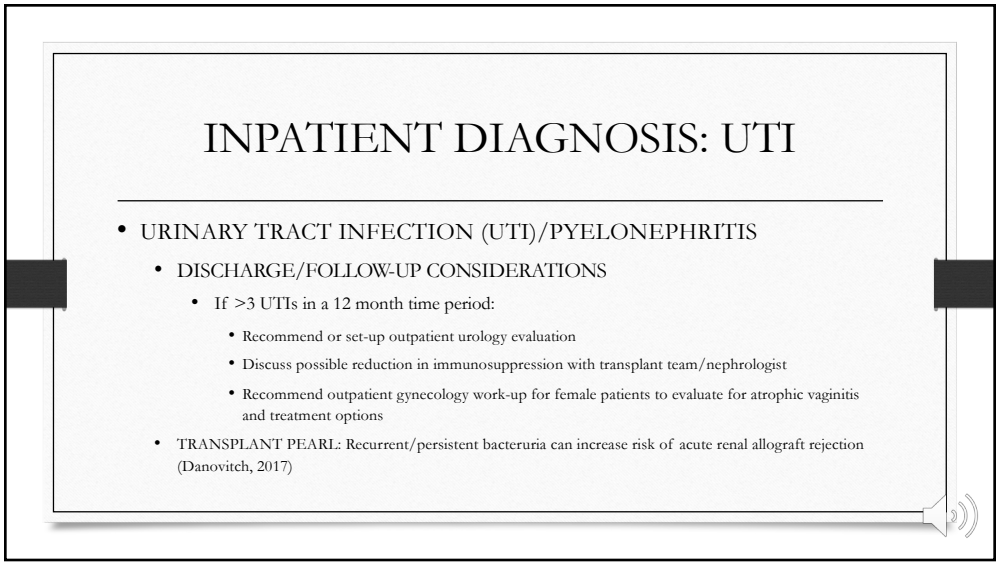
INPATIENT DIAGNOSIS: UTI
• URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
• DISCHARGE/FOLLOW-UP CONSIDERATIONS
• If >3 UTIs in a 12 month time period:
• Recommend or set-up outpatient urology evaluation
• Discuss possible reduction in immunosuppression with transplant team/nephrologist
• Recommend outpatient gynecology work-up for female patients to evaluate for atrophic vaginitis and treatment options
• TRANSPLANT PEARL: Recurrent/persistent bacteruria can increase risk of acute renal allograft rejection (Danovitch, 2017)

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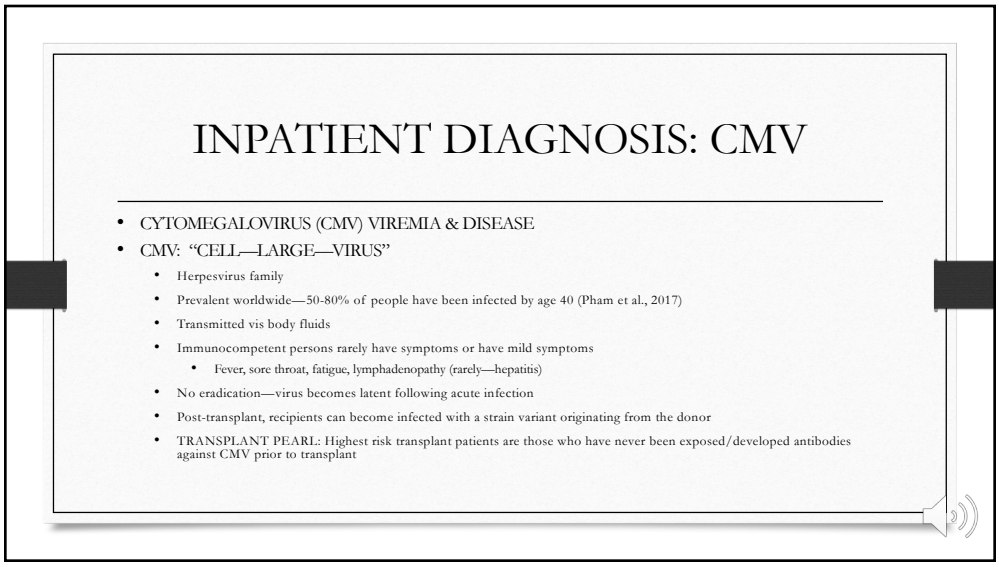
INPATIENT DIAGNOSIS: CMV
CYTOMEGALOVIRUS (CMV) VIREMIA & DISEASE
CMV: "CELL—LARGE—VIRUS"
Herpesvirus family
Prevalent worldwide—50-80% of people have been infected by age 40 (Pham et al., 2017)
Transmitted vis body fluids
Immunocompetent persons rarely have symptoms or have mild symptoms
Fever, sore throat, fatigue, lymphadenopathy (rarely—hepatitis)
No eradication—virus becomes latent following acute infection
Post-transplant, recipients can become infected with a strain variant originating from the donor
TRANSPLANT PEARL: Highest risk transplant patients are those who have never been exposed/developed antibodies against CMV prior to transplant

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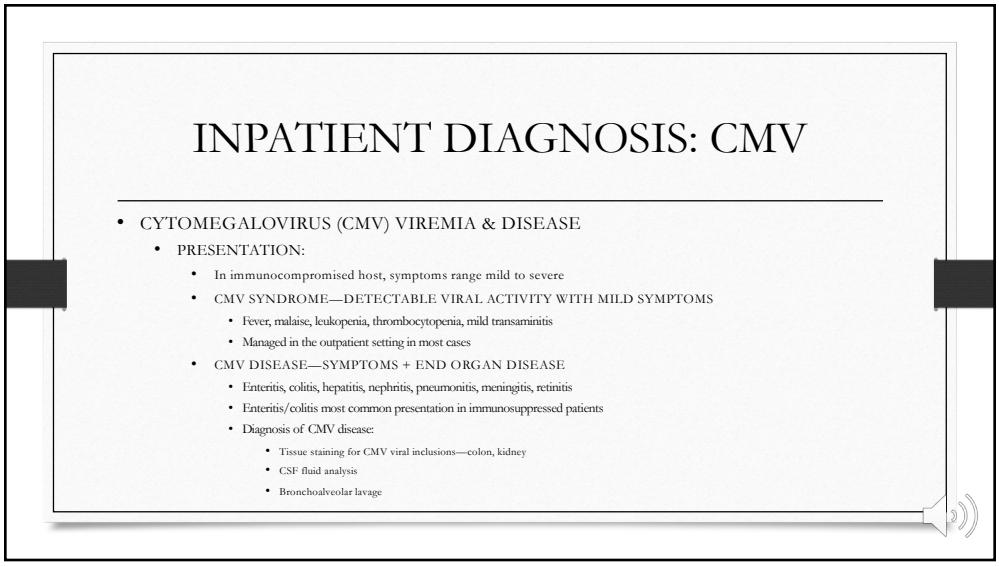
INPATIENT DIAGNOSIS: CMV
CYTOMEGALOVIRUS (CMV) VIREMIA & DISEASE
PRESENTATION:
In immunocompromised host, symptoms range mild to severe
CMV SYNDROME—DETECTABLE VIRAL ACTIVITY WITH MILD SYMPTOMS
Fever, malaise, leukopenia, thrombocytopenia, mild transaminitis
Managed in the outpatient setting in most cases
CMV DISEASE—SYMPTOMS + END ORGAN DISEASE
Enteritis, colitis, hepatitis, nephritis, pneumonitis, meningitis, retinitis
Enteritis/colitis most common presentation in immunosuppressed patients
Diagnosis of CMV disease:
Tissue staining for CMV viral inclusions—colon, kidney
CSF fluid analysis
Bronchoalveolar lavage

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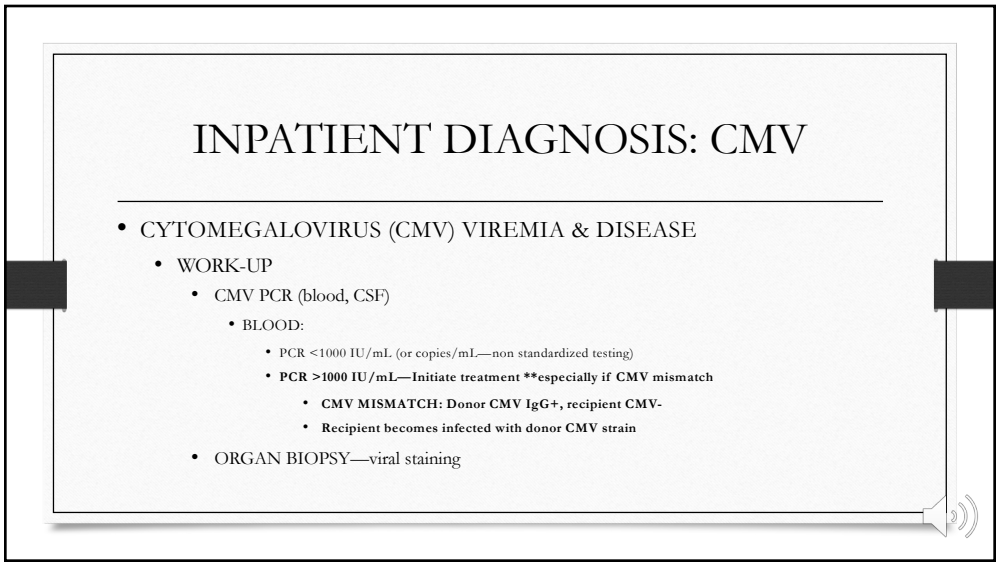
INPATIENT DIAGNOSIS: CMV
CYTOMEGALOVIRUS (CMV) VIREMIA & DISEASE
WORK-UP
CMV PCR (blood, CSF)
BLOOD:
PCR <1000 IU/mL (or copies/mL—non standardized testing)
PCR >1000 IU/mL—Initiate treatment **especially if CMV mismatch
CMV MISMATCH: Donor CMV IgG+, recipient CMV-
Recipient becomes infected with donor CMV strain
ORGAN BIOPSY—viral staining

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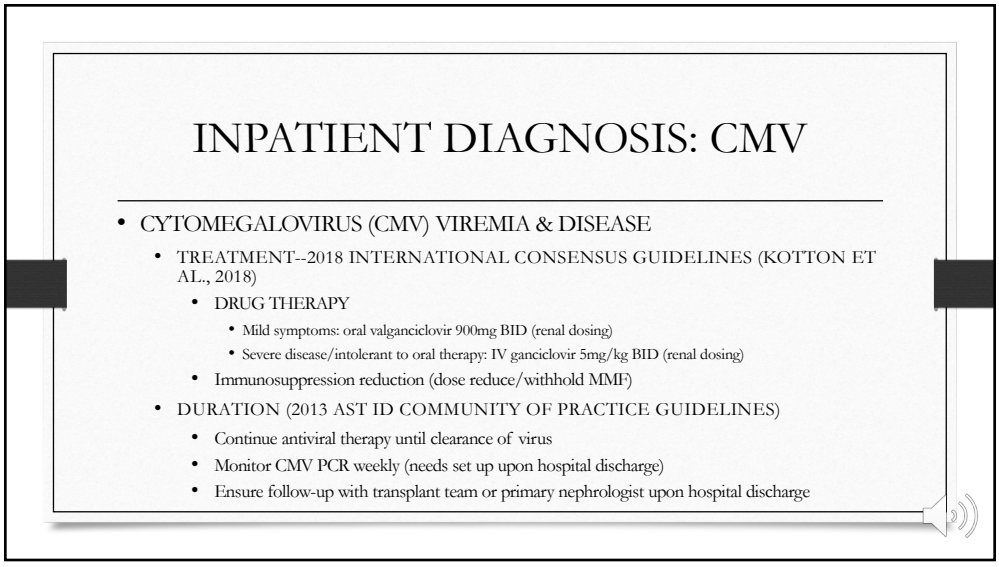
INPATIENT DIAGNOSIS: CMV
CYTOMEGALOVIRUS (CMV) VIREMIA & DISEASE
TREATMENT--2018 INTERNATIONAL CONSENSUS GUIDELINES (KOTTON ET AL., 2018)
DRUG THERAPY
Mild symptoms: oral valganciclovir 900mg BID (renal dosing)
Severe disease/intolerant to oral therapy: IV ganciclovir 5mg/kg BID (renal dosing)
Immunosuppression reduction (dose reduce/withhold MMF)
DURATION (2013 AST ID COMMUNITY OF PRACTICE GUIDELINES)
Continue antiviral therapy until clearance of virus
Monitor CMV PCR weekly (needs set up upon hospital discharge)
Ensure follow-up with transplant team or primary nephrologist upon hospital discharge

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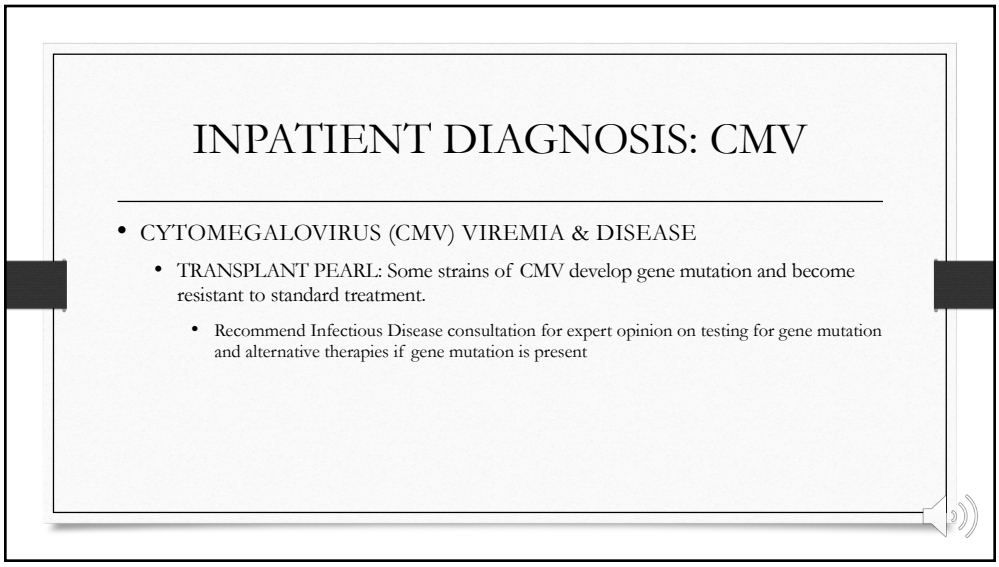
INPATIENT DIAGNOSIS: CMV
• CYTOMEGALOVIRUS (CMV) VIREMIA & DISEASE
• TRANSPLANT PEARL: Some strains of CMV develop gene mutation and become resistant to standard treatment.
• Recommend Infectious Disease consultation for expert opinion on testing for gene mutation and alternative therapies if gene mutation is present

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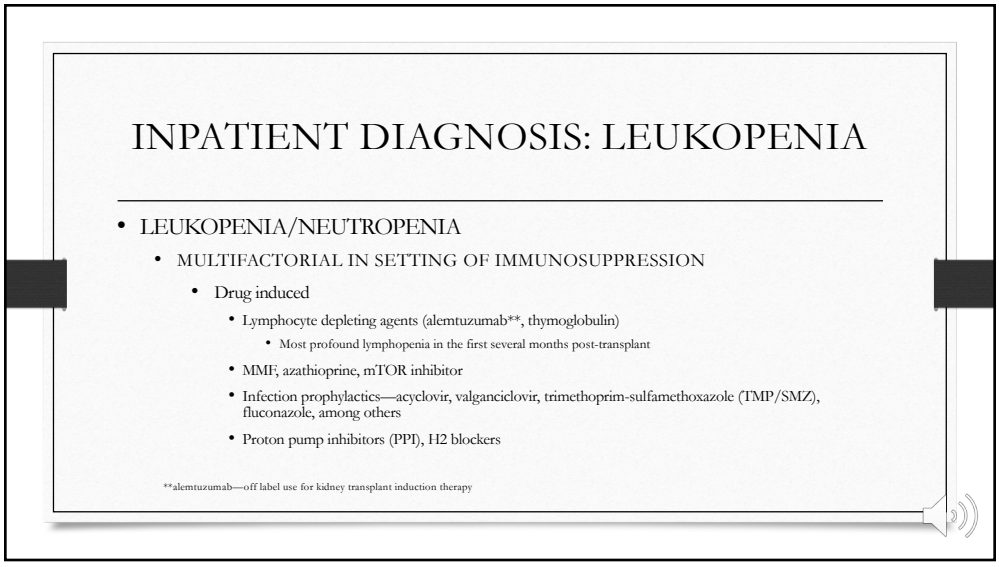
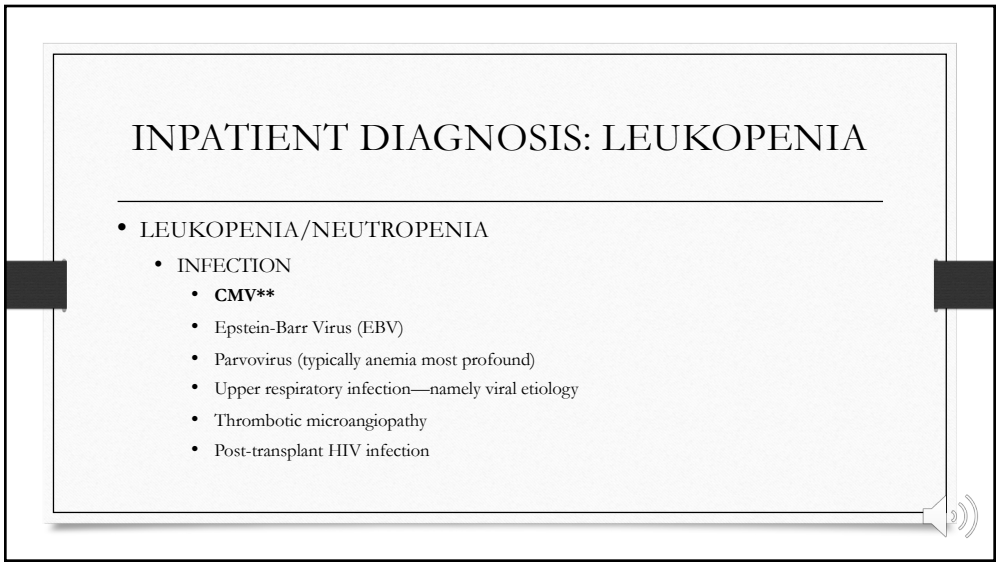

INPATIENT DIAGNOSIS: LEUKOPENIA
• LEUKOPENIA/NEUTROPENIA
• MULTIFACTORIAL IN SETTING OF IMMUNOSUPPRESSION
• Drug induced
• Lymphocyte depleting agents (alemtuzumab**, thymoglobulin)
• Most profound lymphopenia in the first several months post-transplant
• MMF, azathioprine, mTOR inhibitor
• Infection prophylactics—acyclovir, valganciclovir, trimethoprim-sulfamethoxazole (TMP/SMZ), fluconazole, among others
• Proton pump inhibitors (PPI), H2 blockers
**alemtuzumab—off label use for kidney transplant induction therapy

50


INPATIENT DIAGNOSIS: LEUKOPENIA
LEUKOPENIA/NEUTROPENIA
INFECTION
CMV**
Epstein-Barr Virus (EBV)
Parvovirus (typically anemia most profound)
Upper respiratory infection—namely viral etiology
Thrombotic microangiopathy
Post-transplant HIV infection

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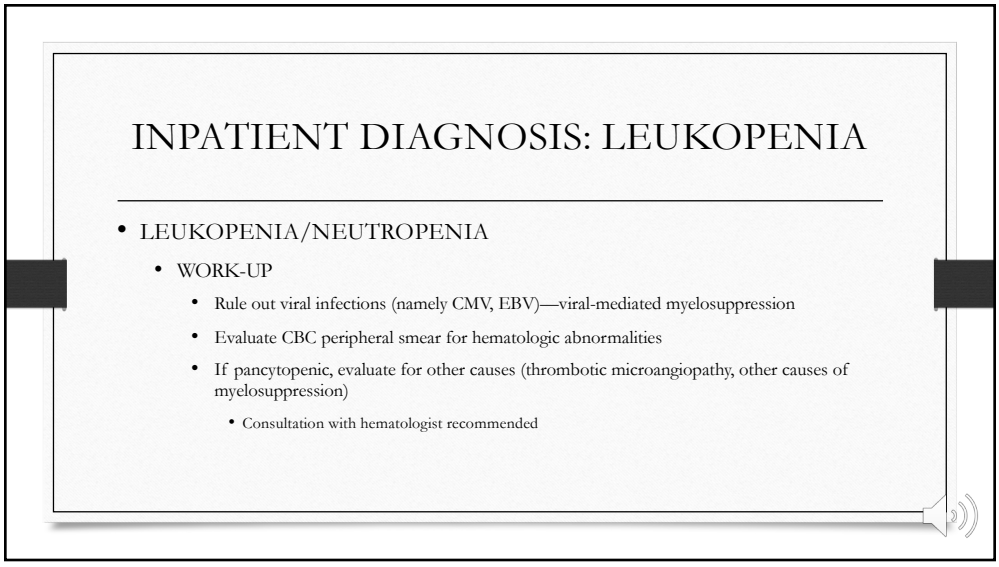
INPATIENT DIAGNOSIS: LEUKOPENIA
LEUKOPENIA/NEUTROPENIA
WORK-UP
Rule out viral infections (namely CMV, EBV)—viral-mediated myelosuppression
Evaluate CBC peripheral smear for hematologic abnormalities
If pancytopenic, evaluate for other causes (thrombotic microangiopathy, other causes of myelosuppression)
Consultation with hematologist recommended

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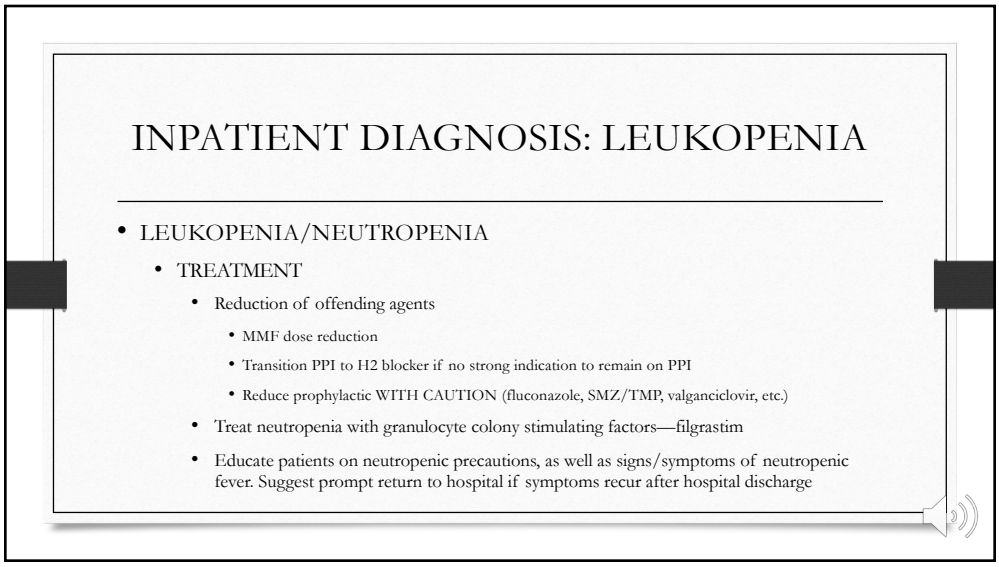
INPATIENT DIAGNOSIS: LEUKOPENIA
• LEUKOPENIA/NEUTROPENIA
• TREATMENT
• Reduction of offending agents
• MMF dose reduction
• Transition PPI to H2 blocker if no strong indication to remain on PPI
• Reduce prophylactic WITH CAUTION (fluconazole, SMZ/TMP, valganciclovir, etc.)
• Treat neutropenia with granulocyte colony stimulating factors—filgrastim
• Educate patients on neutropenic precautions, as well as signs/symptoms of neutropenic fever. Suggest prompt return to hospital if symptoms recur after hospital discharge

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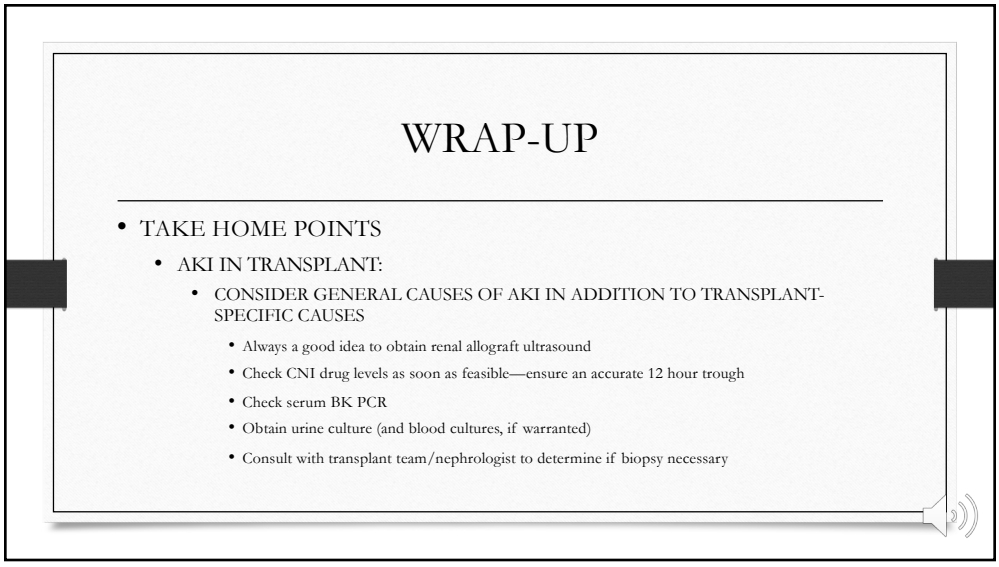
WRAP-UP
• TAKE HOME POINTS
• AKI IN TRANSPLANT:
• CONSIDER GENERAL CAUSES OF AKI IN ADDITION TO TRANSPLANT-SPECIFIC CAUSES
• Always a good idea to obtain renal allograft ultrasound
• Check CNI drug levels as soon as feasible—ensure an accurate 12 hour trough
• Check serum BK PCR
• Obtain urine culture (and blood cultures, if warranted)
• Consult with transplant team/nephrologist to determine if biopsy necessary

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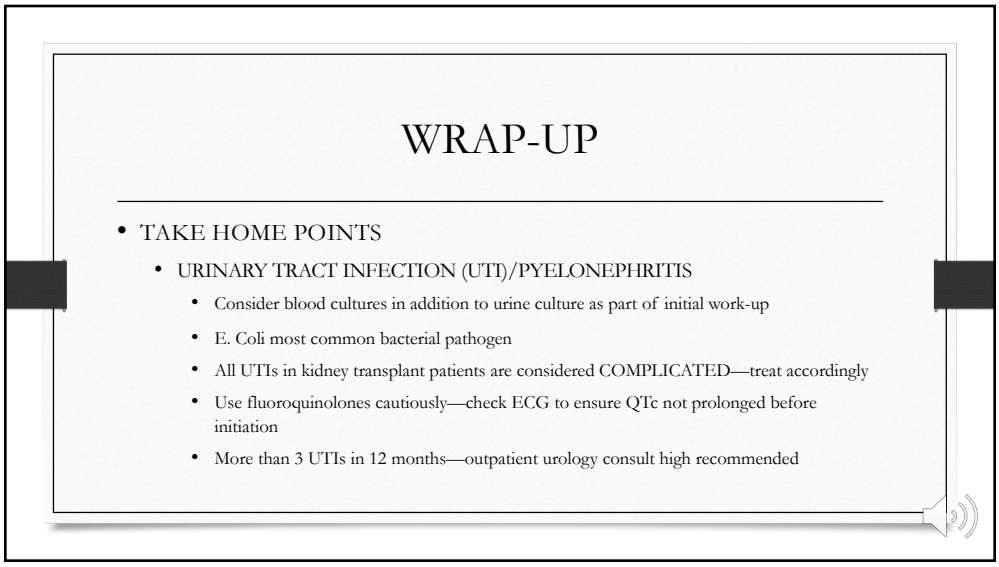
WRAP-UP
TAKE HOME POINTS
URINARY TRACT INFECTION (UTI)/PYELONEPHRITIS
Consider blood cultures in addition to urine culture as part of initial work-up
E. Coli most common bacterial pathogen
All UTIs in kidney transplant patients are considered COMPLICATED—treat accordingly
Use fluoroquinolones cautiously—check ECG to ensure QTc not prolonged before initiation
More than 3 UTIs in 12 months—outpatient urology consult high recommended

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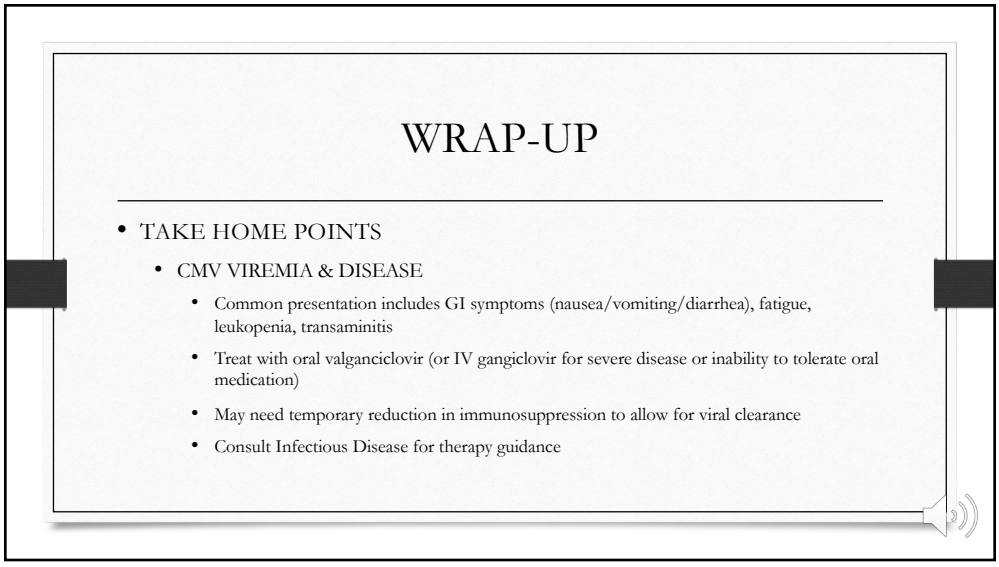
WRAP-UP
TAKE HOME POINTS
CMV VIREMIA & DISEASE
Common presentation includes GI symptoms (nausea/vomiting/diarrhea), fatigue, leukopenia, transaminitis
Treat with oral valganciclovir (or IV gangiclovir for severe disease or inability to tolerate oral medication)
May need temporary reduction in immunosuppression to allow for viral clearance
Consult Infectious Disease for therapy guidance

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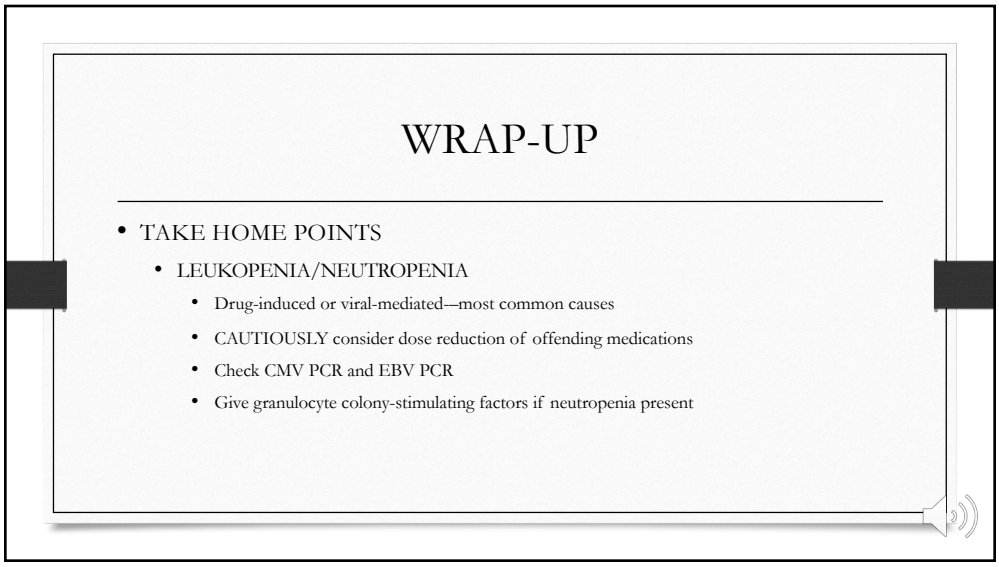
WRAP-UP
TAKE HOME POINTS
LEUKOPENIA/NEUTROPENIA
Drug-induced or viral-mediated—most common causes
CAUTIOUSLY consider dose reduction of offending medications
Check CMV PCR and EBV PCR
Give granulocyte colony-stimulating factors if neutropenia present

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THANK YOU!
QUESTIONS?
park.stephanie@mayo.edu
Please see additional slides for more information on induction therapies, maintenance medications, and prophylactic therapies

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BASIC PRINCIPLES OF IMMUNOSUPPRESSION MANAGEMENT

INDUCTION, MAINTENANCE,
AND INFECTION PROPHYLACTIC THERAPIES

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INDUCTION THERAPY

- RAPID INDUCTION OF IMMUNOSUPPRESSION FROM DAY 0 THROUGH THE FIRST SEVERAL WEEKS POST-KIDNEY TRANSPLANT
- LYMPHOCYTE DEPLETING
  - THYMOGLOBULIN—1.5MG/KG/DAY FOR 4-7 DAYS
    - USED FOR HIGHLY SENSITIZED PATIENTS DUE TO HIGH POTENCY→EFFECT CAN LAST FOR YEARS
  - ALEMTUZUMAB. **OFF LABEL USE IN KIDNEY TRANSPLANT; APPROVED FOR CLL, MS**
    - USED FOR STANDARD INDUCTION IN LESS SENSITIZED PATIENTS
- NON-LYMPHOCYTE DEPLETING
  - BASILIXIMAB
    - USED FOR INDUCTION OF PATIENTS WHO ARE AT RISK FOR MALIGNANCY OR ACTIVATION/WORSENING OF INFECTION
      - AGE >65
      - EBV MISMATCH (RISK OF POST-KIDNEY TRANSPLANT PTLD)
      - HEPATITIS C POSITIVE (PRE-EXISTING HCV)

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MAINTENANCE THERAPY

- SUSTAIN IMMUNOSUPPRESSION (IS) TO AVOID REJECTION
- STANDARD MAINTENANCE IS REGIMEN:
  - CNI + ANTIMETABOLITE +/- CORTICOSTEROID
    - COMMON REGIMEN: TACROLIMUS + MMF +/- PREDNISONE

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CALCINEURIN INHIBITORS (CNI)

- CYCLOSPORINE (CSA)—GOAL DRUG LEVEL 100-200 (IN STABLE/LONGTERM PATIENTS)
- TACROLIMUS (FK, FK506)—GOAL DRUG LEVEL 6-8 (IN STABLE/LONGTERM PATIENTS)
  - TREND IN UNITED STATES—TACROLIMUS
  - CYCLOSPORINE HISTORY:
    - DEVELOPED FROM 2 STRAINS OF FUNGI IN SOIL FROM SWITZERLAND
    - FIRST USED IN ENGLAND IN THE 1970S, IN THE US IN THE 1980S
    - REVOLUTIONIZED FIELD OF TRANSPLANT—KIDNEY, LIVER, HEART, PANCREAS, AND LUNG
  - TACROLIMUS HISTORY:
    - DEVELOPED FROM SOIL ORGANISMS IN JAPAN
    - FIRST USED IN THE US IN THE 1990S AT UNIVERSITY OF PITTSBURGH
      - FDA APPROVED 1994 (LIVER), 1997 (KIDNEY), 2006 (HEART)
    - LESS EPISODES OF REJECTION VS. CSA
    - AS OF 2013, 90% OF ADULT KIDNEY TRANSPLANT MAINTENANCE IS INVOLVES USE OF FK

****FK IS 10-100 TIMES MORE POTENT THAN CSA IN ITS IMMUNOSUPPRESSANT EFFECTS****

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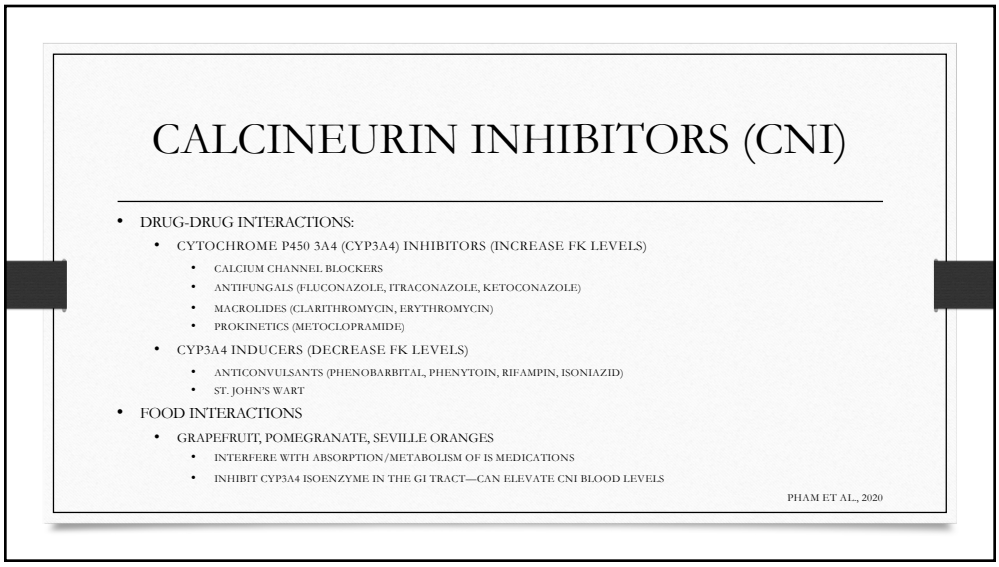
CALCINEURIN INHIBITORS (CNI)
DRUG-DRUG INTERACTIONS:
CYTOCHROME P450 3A4 (CYP3A4) INHIBITORS (INCREASE FK LEVELS)
CALCIUM CHANNEL BLOCKERS
ANTIFUNGALS (FLUCONAZOLE, ITRACONAZOLE, KETOCONAZOLE)
MACROLIDES (CLARITHROMYCIN, ERYTHROMYCIN)
PROKINETICS (METOCLOPRAMIDE)
CYP3A4 INDUCERS (DECREASE FK LEVELS)
ANTICONVULSANTS (PHENOBARBITAL, PHENYTOIN, RIFAMPIN, ISONIAZID)
ST. JOHN'S WART
FOOD INTERACTIONS
GRAPEFRUIT, POMEGRANATE, SEVILLE ORANGES
INTERFERE WITH ABSORPTION/METABOLISM OF IS MEDICATIONS
INHIBIT CYP3A4 ISOENZYME IN THE GI TRACT—CAN ELEVATE CNI BLOOD LEVELS
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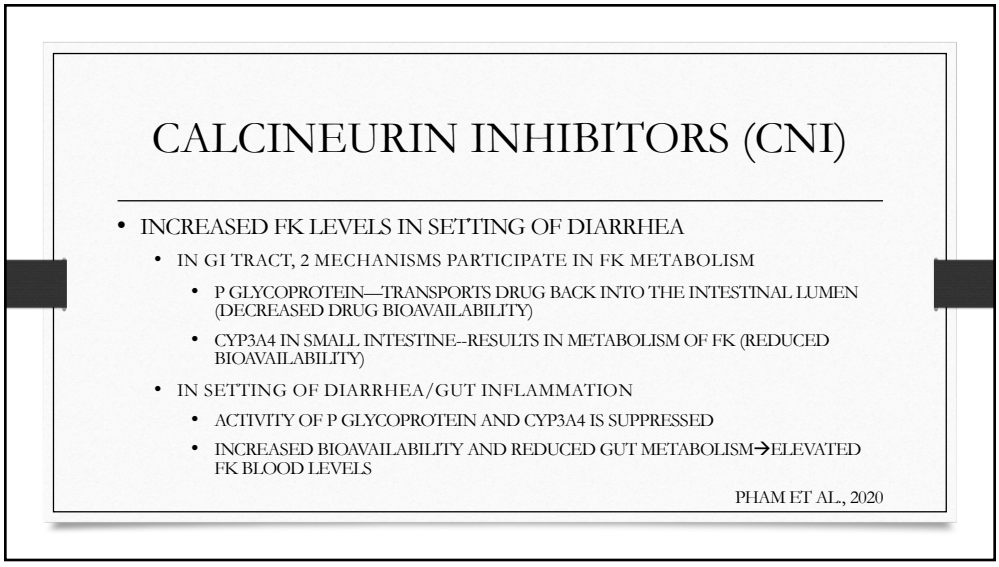
CALCINEURIN INHIBITORS (CNI)
INCREASED FK LEVELS IN SETTING OF DIARRHEA
IN GI TRACT, 2 MECHANISMS PARTICIPATE IN FK METABOLISM
P GLYCOPROTEIN—TRANSPORTS DRUG BACK INTO THE INTESTINAL LUMEN (DECREASED DRUG BIOAVAILABILITY)
CYP3A4 IN SMALL INTESTINE--RESULTS IN METABOLISM OF FK (REDUCED BIOAVAILABILITY)
IN SETTING OF DIARRHEA/GUT INFLAMMATION
ACTIVITY OF P GLYCOPROTEIN AND CYP3A4 IS SUPPRESSED
INCREASED BIOAVAILABILITY AND REDUCED GUT METABOLISM→ELEVATED FK BLOOD LEVELS
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ADJUNCTIVE AGENTS--ANTIMETABOLITES

- MMF
  - HISTORY
    - DEVELOPED FROM PCN BREVICOMPACTUM AND FUNGI IN THE 1890S
    - HAD POOR ANTIBACTERIAL AND ANTIFUNGAL PROPERTIES
    - LATER FOUND TO HAVE IS PROPERTIES
    - HUMAN TRIALS IN THE 1980S—50% REDUCTION IN TRANSPLANT REJECTION
    - BY 2002, MOST WIDELY PRESCRIBED IS IN THE US
    - APPROVED FOR COMBINATION THERAPY WITH FK IN 2009
  - SIGNIFICANT GI SIDE EFFECTS
    - LED TO DEVELOPMENT OF ENTERIC COATED FORMULATION (MYCOPHENOLATE SODIUM)
      - DELAYED ABSORPTION→BYPASS STOMACH AND SMALL BOWEL

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ADJUNCTIVE AGENTS--ANTIMETABOLITES

- MMF (CONT'D)
  - SIDE EFFECTS:
    - GI TOXICITY—NAUSEA, VOMITING, DIARRHEA
    - LEUKOPENIA/NEUTROPENIA
    - ANEMIA
    - THROMBOCYTOPENIA
  - ROUTINE DOSING:
    - MYCOPHENOLATE MOFETIL: 1000MG PO BID
    - MYCOPHENOLATE SODIUM: 720MG BID
  - SPECIAL CONSIDERATIONS
    - **NOT SAFE IN PREGNANCY**
      - RECOMMEND CONTRACEPTIVE DURING ENTIRETY OF MMF EXPOSURE, PLUS 6 WEEKS BEYOND DISCONTINUATION OF DRUG

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ADJUNCTIVE AGENTS—mTOR INHIBITORS

- SIROLIMUS, EVEROLIMUS
  - USED MINIMALLY AT MCA
  - CAN CAUSE DELAYED WOUND HEALING
    - STOP 1-2 WEEKS AHEAD OF PLANNED SURGERIES, RESUME WHEN COMPLETELY HEALED
  - POTENTIAL BENEFITS
    - ANTI-TUMOR EFFECTS
      - SIROLIMUS—NON-MELANOMA SKIN CANCER
      - EVEROLIMUS—USED IN TREATMENT OF BREAST CANCER, RENAL CELL CARCINOMA, NEUROENDOCRINE TUMORS

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CORTICOSTEROIDS

- PREDNISONE
  - ROUTINE DOSING—5MG/DAY
  - TO USE OR NOT TO USE:
    - INDIVIDUALIZED BASED ON IMMUNOLOGIC RISK FACTORS
      - HIGH PANEL REACTIVE ANTIBODY (PRA)
      - PRESENCE OF DONOR SPECIFIC ANTIBODIES
      - RISK OF ORIGINAL DISEASE RECURRENCE
        - IgA NEPHROPATHY, FSGS, C3 GN, LUPUS NEPHRITIS
      - METHOD OF IS INDUCTION
        - BASILIXIMAB (AGE >65, EBV MISMATCH, HCV+)

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NON-CNI BASED MAINTENCE REGIMEN

- BELATACEPT
  - MAINTENANCE ONLY—NOT INDICATED FOR INDUCTION OR RESCUE/REJECTION THERAPY
  - BENEFIT TRIAL
    - INTERNATIONAL STUDY COMPARING CSA VS BELATACEPT
      - STANDARD CRITERIA KIDNEYS:
        - USE OF BELATACEPT ASSOCIATED WITH INCREASED PATIENT AND GRAFT SURVIVAL AND IMPROVEMENT IN KIDNEY FUNCTION (INCREASED eGFR) OVER 7 YEAR TIME FRAME
      - EXTENDED CRITERIA KIDNEYS:
        - USE OF BELATACEPT SHOWED INCREASED KIDNEY FUNCTION
        - NO DIFFERENCE IN OUTCOMES VS. CSA THERAPY OVER 7 YEARS

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NON-CNI BASED MAINTENANCE REGIMEN

- BELATACEPT (CONT'D)
  - DOSING:
    - IV, ONCE MONTHLY (28 DAYS +/- 3), WEIGHT BASED—5MG/KG
    - GIVEN IN CONJUNCTION WITH ADJUNCTIVE (MMF) AND PREDNISONE--FDA APPROVED REGIMEN
  - INCREASED RISK OF PTLD IN EBV IgG NEGATIVE PATIENTS (BENEFIT TRIAL)—CONTRAINDICATED
  - SOME CONCERN FOR REJECTION VS CNI--ANY DONOR SPECIFIC ANTIBODY MFI >2000—NOT ACCEPTABLE
  - BLACK BOX WARNING--NOT RECOMMENDED IN LIVER TRANSPLANT RECIPIENTS—INCREASED RISK OF GRAFT LOSS AND DEATH

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INFECTION PROPHYLAXIS REGIMEN EXAMPLE**

- FUNGAL (COCCIDIOIDOMYCOSIS)
  - FLUCONAZOLE X 1 YEAR; INDEFINITELY IF COCCI AB+
- BACTERIAL (PJP PNA, UTI)
  - SS BACTRIM X 6 MONTHS (ALTERNATIVES—DAPSONE, PENTAMIDINE)
- ANTIVIRAL (HSV, CMV)
  - DONOR-/RECIPIENT- --ACYCLOVIR X 1 MONTH
  - DONOR+/RECEIPIENT+ OR D-/R+ --VALGANCICLOVIR X 3 MONTHS
  - DONOR+/RECIPIENT- (MISMATCH) --VALGANCICLOVIR X 6 MONTHS
    - **HIGHEST RISK FOR COMPLICATIONS AND SEVERE CMV DISEASE**

**THIS IS AN EXAMPLE ONLY. PROPHYLACTIC REGIMENS VARY FROM CENTER TO CENTER AND TYPICALLY TAKE INTO ACCOUNT LOCAL RISK FACTORS

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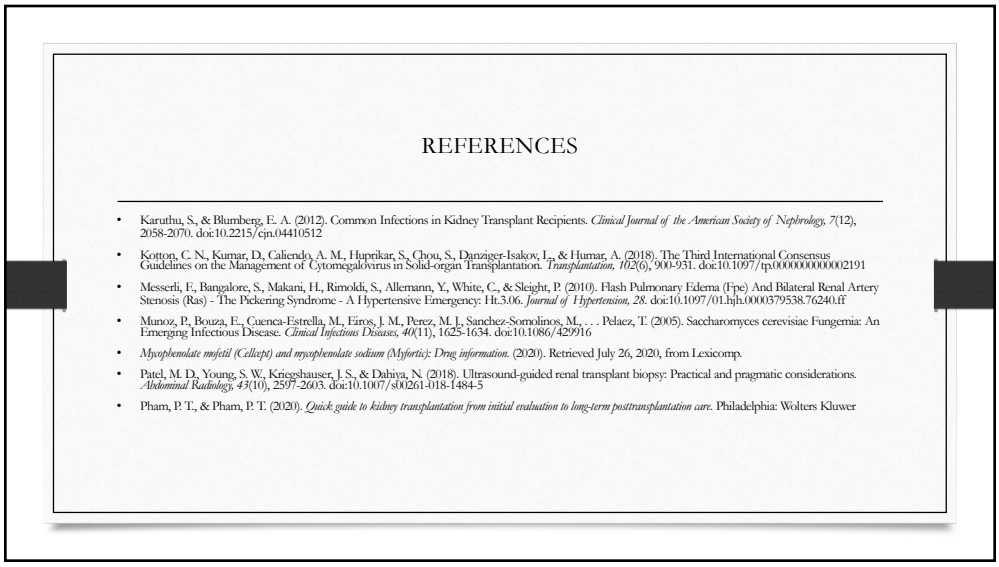
MANAGEMENT OF THE HOSPITALIZED
KIDNEY TRANSPLANT PATIENT



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