Transplant Infectious Disease Update May 3, 2024 Jeremey Walker M.D.	
Assistant Professor Transplant Infectious Diseases	
<b>Disclosures</b>	
I have no financial disclosures.	
LIGHT STATEMENT HEREING HEREIN SOCIOL OF HEICHE	
Learning Objectives	
Differentiate level of risk for preventable infections amongst transplant recipients, specifically CMV and PJP.	
Recognize complications of prophylactic medications and identify next steps in management	
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Outline	4	
<ul><li>Cytomegalovirus</li><li>Background</li><li>Prevention strategies</li><li>Cases</li></ul>		
<ul><li>Pneumocystis</li><li>Background</li><li>Prevention strategies</li><li>Cases</li></ul>		
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Cytomegalovirus	5	
<ul> <li>Member of herpes virus family</li> <li>Seroprevalence ~ 50% in US</li> <li>Presence of antibody = latent infection</li> </ul>		
Primary infection generally self-limited febrile illness in childhood		
LICE PLANTAGE BERNSLAM HEIDERN SCHOOL OF HEIDERN HEIDERN SCHOOL OF HEIDERN	at Night Pissons	
	6	
Where does CMV come from?		
Why have I never heard of this before?		
The the America of		

# A helpful example Varicella / Chickenpox Many patients have context of chickenpox and shingles rashes • Example of viral latency and reactivation THE UNIVERSITY OF **Timing of Infection** CMV Prophylaxis CMV Disease Highest Immune Suppression Transplant 6 months **CMV** disease CMV Viremia CMV Syndrome Tissue Invasive Disease

Mono-like liness  - Fear, fatigue mystigss  - Lasts, LET Accommission, 2.X ULNs, abypical lymphocytes, ynsphoperia, thrombosytopenia  Transplant patients  **GOR, of CMV disease in transplant patients prosents in this form  **Telephone (bacterial, fungal, virial) - PTLD - Carcifovascular events - New onset-disbeties mellitus - Nuclear respection - Mortality  **Mortality Accommission - Mortality  **Who is at Risk  Antibodies = Latency  Donor (+) / Recipient (+) Donor (-) / Recipient (+) Donor (-) / Recipient (-)  ***Ges in lateful accommission and the first of the second accommission and the second accommission accommission and the second accommissi	CMV Syndrome		10	
- Lates LFT absorbance and the Card AV May a stylical hymphocytes, hymphopenic from the composition of the c	Mono-like illness			 
Indirect Effects  Indirect Eff	<ul> <li>Fever, fatigue, myalgias</li> </ul>			
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* Acute rejection required for these indirect effects  * Mortality  ***Cotton And J Traditional Traditional Section of the Control of the Con	<ul> <li>New onset- diabetes n</li> </ul>	nellitus	Usaal	
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Who is at Risk  Antibodies = Latency  Donor (+) / Recipient (+)  Donor (+/-) / Recipient (+)  Donor (-) / Recipient (-) ***	<ul> <li>Mortality</li> </ul>			 
Who is at Risk  Antibodies = Latency  Donor (+) / Recipient (+)  Donor (+/-) / Recipient (+)  Donor (-) / Recipient (-) ***				
Who is at Risk  Antibodies = Latency  Donor (+) / Recipient (+)  Donor (+/-) / Recipient (+)  Donor (-) / Recipient (-) ***	Kotton Am J Tx.doi.10.1111/ajt.12006			
Antibodies = Latency  Donor (+) / Recipient (-)  Donor (+/-) / Recipient (+)  Donor (-) / Recipient (-) ***  ""Low risk initially—at risk for natural acquisition post-transplant		HEERSPIK SCHOOL OF MEDIONE GLIBB AN	Rights Preserved	
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Donor (+) / Recipient (-)  Donor (+/-) / Recipient (+)  Donor (-) / Recipient (-) ***  The property of the pro				
Donor (+) / Recipient (-)  Donor (+/-) / Recipient (+)  Donor (-) / Recipient (-) ***  The property of the pro	Antiboo	dies = Latency		 
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*** Low risk initially— at risk for natural acquisition post-transplant	Risk			
		Donor (-) / Recipient (-)		
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#### **Additional Risk Factors** · Lymphocyte depletion · Allograft rejection · Type of transplant • Lung among highest risk · Severe illness or infection THE UNIVERSITY OF ALL ARAMA AT REMANICHAM Prevention Virus persists lifelong, mostly in latency Transmission will occur with organ from CMV positive donor · No vaccine currently available Antivirals · Valganciclovir 900mg daily (preferred) Letermovir 480mg daily (there are additional antiviral options used for treatment of drug resistant infections Maribavir, Foscarnet, Cidofovir) THE UNIVERSITY OF ALL ARMAN AT REMANGHAM **Methods of Prevention** Treatment Dose Valganciclovir Weekly CMV monitoring Preemptive Monitoring Highest Immune Suppression Daily Valganciclovir Prophylaxis Highest Immune Suppression Transplant LICE THE UNIVERSITY OF

#### **Preemptive Monitoring vs Prophylaxis** TABLE 2 Characteristics of antiviral prophylaxis and preemptive therapy Yes (based on fewer and smaller trials), including D+/ R- kidney and liver recipients More difficult to coordinate Viral load thresholds not defined; each program shoul develop viral load thresholds for various clinical indications Common in CMV D+/R- transplant recipier prophylaxis delayed-onset CMV disease) Lesser drug toxicity with shorter courses of antiviral therapy Very limited data Razonable et. al. DOI: 10.1111/ctr.13512 LIFE LINEVERS TY OF BRAINGHAM Case 1 65 year-old with liver transplant for MASLD 5 months prior returns to clinic for routine follow-up. He has done well. CMV serologies Donor (+) / Recipient (-). He is having leukopenia and you are concerned valganciclovir is contributing. Which of the following would be your next step in management? A) Stop prophylaxis as sufficient course has been provided B) Stop prophyaxis and move to preemptive monitoring protocol C) Transition prophylaxis to letermovir D) Decrease to low dose valganciclovir (450mg daily) E) Provide dose filgastrim THE UNIVERSITY OF ALL ARMAN AT BREAKINGHAM How long for prophylaxis? Liver Kidney Heart Lung D+/R-3-6 6 3-6 6-12 R+ 3 6 3 3 Values in Months

Kotton et. al. DOI: 10.1097/TP.00000000000002191

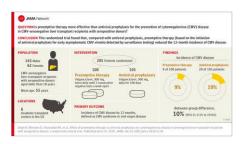
#### If moving to preemptive protocol when would we $\ _{\mid \circ }$ treat?

Population	Threshold	Comments	Reference
High risk D+R-			1,885
39 D+R- SOT (23 kidney, 15 liver, 1 heart)	1500 IU/mL in plasma	No episodes of symptomatic CMV disease were diagnosed in patients with viral loads below 1500 IU/mL. Very high rate of infection (36/39).	195
Mixed risk D+R- and R+			
689 kidney (n = 368) and liver (n = 321), 11% D+R-, 71% R+	3000 copies/mL in whole blood, twice a week (same group later converted this to 2520 IU/mL <sup>196</sup> see below)	More of a study of preemptive therapy and effect of immunity than analysis of threshold	172
3/45 D+R- 42/45 D+R+ SOTR	2275 IU/mL (2500 copies/mL) in plasma	This threshold allowed for discrimination between self-clearing infections and those requiring therapy. Focus of study on use of CMV DNAemia vs antigenemia.	197
59 Kidney, liver, HSCT patients (minority were higher risk)	2520 ILVmL (3000 copies/mL) of whole blood	Whether antiviral treatment needed for PET @ 2520 IU/mL (yes); not an analysis of best threshold, but whether 2520 IU/mL is an effective threshold (yes).	196
Lower risk R+			
252 R+ SOTR	3983 ILVmL threshold resulted in 99.6% NPV, "the great majority of patients at lower risk will not develop CMV disease without specific antivirol theraps".	Analysis of best threshold; single center and only seropositive recipients	198

Kotton et. al. DOI: 10.1097/TP.0000000000002191

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#### Letermovir Prophylaxis?

- Matched control paper (small numbers)
  - Noninferior in preventing CMV disease
  - · Leukopenia improved
  - Tacrolimus increased (recommended 50% reduction when starting)
- RCT in JAMA for high risk Renal Transplant Recipients
  - Noninferior in preventing CMV disease
  - Less leukopenia

Winstead et. al. DOI: 10.1111/tid.13570 Limaye et. al. doi:10.1001/jama.2023.9106

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## **Letermovir Side Effects** • Drug-drug interactions with tacrolimus Nausea / abdominal pain Peripheral edema PREVYMIS™ Cost and coverage may be a barrier Does not cover other herpes viruses THE UNIVERSITY OF ALL ARAMA AT REMANICHAM Low Dose Valganciclovir • Practice sometimes called "mini-dosing" AST guidelines recommend against this practice in any circumstance • Consensus guidelines from 2018 qualify that data is very limited to retrospective studies in low risk patients & also do not recommend Would avoid this approach given the risk for drug resistance development and alternatives available. Management of leukopenia beyond stopping valganciclovir Filgastrim administration Reduction of IS if able, particularly MMF · Addressing other marrow suppressive medications

Case 1	25	
65 year-old with liver transplant for MASLD 5 months prior returns to clinic for routine follow-up. He has done well. CMV serologies Donor (+) / Recipient (-).		
He is having leukopenia and you are concerned valganciclovir is contributing.		
Which of the following would be your next step in management?	A.A.	
A) Stop prophylaxis as sufficient course has been provided     B) Stop prophyaxis and move to preemptive monitoring		
protocol C) Transition prophylaxis to letermovir D) Decrease to low dose valganciclovir (450mg daily)		
E) Provide dose filgastrim		
L 2 THE UNIVERSITY OF HERMANNAM HETESTAK SCHOOL OF MEDICAL	G LLM, ER Ryth Februral	
Case 2	28	
35 year-old with kidney transplant for PKD 2 years prior who	presented for	
routine outpatient follow-up. Stable immune-suppression and course uncomplicated. Feel the weather for the last 24 hours with some URI symptoms. I something is going through the elementary school and both	ing a little under Reports Children have	
been sick. Routine labs unremarkable.  72 hours later a CMV quant from whole blood returns 500 IU learn she feels back to normal.		
Initial Serologies Donor + / Recipient + and completed 3 mon prophylactic valganciclovir. She lives in Mobile.	ths of	
What would be your next step in management?  A) Nothing further, 6 month follow-up		
B) Arrange for CMV DNA in Mobile in 1 week     Initiate valganciclovir at prophylactic dose		
D) Initiate valganciclovir at treatment dose		
FETSIN SCHOOL OF MIDDING	© LLSIN 23 Rights Paramorel	
CMM/As aking a surking a	27	
CMV testing options		
<ul> <li>CMV IgM/ IgG – mainly used pre-transplant, occasionally look for s</li> <li>CMV T-cell immunity assay – used to assess immune response,</li> </ul>	eroconversion post	
CMV viral culture – costly and poor sensitivity		
CMV antigenemia – limitations in leukopenia, technically complica standardize	ted, difficulty to	
CMV QNAT testing (DNA)—the current "gold standard"		
		_
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### **CMV QNAT** Whole Blood • Positive earlier • Higher quantity/ mL Plasma • Better predictor for relapse when Centrifugation positive UAB testing runs on whole-blood Consistency is key Whole blood THE UNIVERSITY OF ALL ARAMA AT REMANICHAM **CMV QNAT Standards** · Standard should be reported as IU/mL • 1 IU/ mL = 1.72 copies/ mL · Check values 1-week apart • 3 fold increase (0.5 log) required to be significant \* 5 fold increase (0.7 log) required when viral load $\leq$ 1000 WHO standard for Lower Limit of Quantification is 200 IU/mL Limaye et al. CMR https://doi.org/10.1128/CMR.00043-19. Reasons to Order CMV QNAT Concern for Tissue invasive disease Beware false negatives Gl disease Lung Transplant with pneumonitis Very rare in highest risk patients Concern for CMV syndrome Sent as part of work-up for acute event with better · Pre-emptive Protocol alternative found. Monitoring response to therapy Surveillance after prophylaxis no data to support, general consensus (if done)≤ 12 weeks THE UNIVERSITY OF THE STATE OF

Approach to Positive Result	31	
1, Determine pre-test probability		
Reason test was sent		
Patients risk factors for CMV		
Is there an alternative explanation		
2, Consider CMV QNAT value		
Some pre-emptive protocols begin 1,500-3,000 IU/mL     UAB uses highly sensitive assay (200 IU/mL standard LLD)		
Trend most valuable piece of information		
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HETSSEK SCHOOL OF METCHNE EW	25. 4.8 Rights Passervel.	
Case 2	12	
35 year-old with kidney transplant for PKD 2 years prior who presented	for	
35 year-old with kidney transplant for PKD 2 years prior who presented routine outpatient follow-up. Stable immune-suppression and course uncomplicated. Feeling a little uthe weather for the last 24 hours with some URI symptoms. Reports something is going through the elementary school and both children harbeen sick. Routine labs unremarkable.	ınder	
72 hours later a CMV quant from whole blood returns 500 IU/mL. You ca learn she feels back to normal.	II and	
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A) Nothing further, 6 month follow-up     B) Arrange for CMV DNA in Mobile in 1 week		
C) Initiate valganciclovir at prophylactic dose D) Initiate valganciclovir at treatment dose	May 1	
	<b>5</b>	
HELPARKETY OF THE PROPERTY OF	III 48 Rights Preserved	
Case 3	п	
55 YO with heart transplant for NICM 9 months prior was found to have QNAT 2,000 IU/mL. Serologies D(+) / R (-) and he completed 6 months o prophylaxis with valganciclovir. You restart valganciclovir at treatment do and schedule follow-up labs in one week.	f	,
Follow-up labs in one week return with CMV QNAT of 5,000 IU/mL. Patie remains asymptomatic and is otherwise doing well.	ent	
What is your next step in management?  A) Continue valganciclovir at current dose		
B) Review valganciclovir dosing with pharmacist		-
C) Admit for IV Ganciclovir D) Admit for IV Foscarnet		
E) Start oral Maribavir		
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Case 3	24	
B) Review valganciclovir dosing with pharmacist		
<ul> <li>Dosing is titrated significantly based off GFR</li> <li>Cerner is a poor predictor of GFR</li> <li>If kidney dysfunction present, would consider reviewing dosing be starting – underdosing may predispose to drug resistance</li> </ul>	ofore	
LICE THE THE THE PROPERTY HEREIN LOCAL OF HECKE.	115-ph/frances	
Drug Resistant CMV	35	
Foscarnet     High nephrotoxicity, electrolyte wasting     IV only, requires inpatient monitoring		
Cidofovir High nephrotoxicity IV only		
<ul> <li>Maribavir</li> <li>Oral and minimal toxicity</li> <li>Altered taste in ~ half of patients although to varying degree</li> <li>May fail with high viral replication</li> </ul>		
LOCAL MAINA AT INTERMEDIAN HETSEN SCHOOL OF MEDICAL	All tights Processed	
Case 3	36	
55 YO with heart transplant for NICM 9 months prior was found to have CMV QNAT 2,000 IU/mL. Serologies D(+) / R (-) and he completed 6 months of prophylaxis with valganciclovir. You restart valganciclovir at treatment dose and schedule follow-up labs in one week.		
Follow-up labs in one week return with CMV QNAT of 5,000 IU/mL. Patient remains asymptomatic and is otherwise doing well.		
What is your next step in management?		
Continue valganciclovir at current dose		
(assuming you checked with pharmacy already)		
May take 2 weeks to reac		
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CMV Key Points	
<ul> <li>Risk defined by Serologies and Type of Transplant</li> <li>D+ / R - highest risk</li> <li>Lung transplant highest risk</li> </ul>	
<ul> <li>Prevention strategies include Prophylaxis vs Preemptive monitoring</li> <li>UAB uses prophylaxis, which makes it the best option for our patients</li> <li>There is a role for monitoring though in select cases</li> </ul>	
Valganciclovir may worsen leukopenia There are numerous strategies to address this, guided by patient factors There are some institutional guidelines in place, but low threshold to engage TxID if concerns or questions	
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Case 4	
40 y/o female with liver transplant 9 months prior for AIH presents with dyspnea.  Transplant course complicated by CMV syndrome at 8 months and recent elevated liver enzymes treated with increased steroids.  She has 1 week of fatigue, dry cough, and increasing dyspnea. She was admitted and quickly escalated to 6L NC.	
You are the overnight admitting team & can send one test to confirm your suspicion-What would you send?  A) CMV QNAT  B) Beta-D-Glucan C) Urine histoplasma antigen	
D) I can't answer till I complete my med-rec	
Pneumocystis	
<ul> <li>Opportunistic fungal pathogen</li> <li>Transmitted through person-person spread</li> <li>Symptomatic disease limited to severely immune-suppressed</li> </ul>	
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Timing of Infection	40	
Without prophylaxis		
<ul><li>Most occurred within first 6 months</li><li>Rates 5-15%</li></ul>		
<ul> <li>Prophylaxis now universal immediately post-transplant occurring later, typically at times of increased risk</li> </ul>	so disease	
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	48	
PJP Risk Factors	at at	
a Lung transplant		
<ul><li>Lung transplant</li><li>Lymphopenia</li></ul>		
CMV infection		
Hypogammaglobulinemia		
Graft rejection		
Older age		
Corticosteroids		
Fishman.etal. DOI: 10.1111/ctr.13587		
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	42	
PJP Clinical Presentation	1	
Table 2. Signs and symptoms of <i>Pneumocystis</i> pneumonia		
Sign or Symptom of PJP Incidence		
Fever 81%-87%  Dyspnea 66%-68%		
Cough 71%-81%	0-046	
Chest pain 23%-24% Abnormal lung auscultation on examination 30%-34%		
Abnormal chest radiography 92%-96% Hypoxemia 78%-91%	769	
The same of the sa	Par Tall	
Presentations often more rapid in development and severe than case studies		
describing disease in patients with AIDS		
Fishman et. al. DOI: 10.1111/ctr.13587		
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40 y/o female with liver transplant 9 months prior for AIH presents with	
dyspnea.  Transplant course complicated by CMV syndrome at 8 months and recent	
elevated liver enzymes treated with increased steroids.  She has 1 week of fatigue, dry cough, and increasing dyspnea. She was	
admitted and quickly escalated to 6L NC.	
You are the overnight admitting team & can	
send one test to confirm your suspicion- What would you send?	
A) CMV QNAT	
B) Beta-D-Glucan C) Urine histoplasma antigen	
D) I can't answer till I complete my med-rec	
LEGISLAND BERKESAN HEFSEN SCHOOL OF MEDICAL SERVICE STATE AND	
Prophylaxis	
40.007	
All SOT recipients should receive 6-12 months     Lung transplant – lifelong	
Prior PJP – lifelong	
Heart may extend to lifelong	
Any SOTR with risk factors (rejection, CMV disease, flare of	
autoimmune disease) may consider restarting	
Bactrim is the preferred agent. Would not expect PJP disease if on Bactrim	
prophylaxis.	
U-2 THE MATERIAL STATE OF MIXTURE CONTROL OF MIXTUR	
A ALBAMA O' BENNIGAM PERSON OF PERSON  COST OF	
Bactrim (Trimethoprim/ sulfamethoxazole)	
Side Effects	
Bone Marrow Suppression	
Rash (including SJS)     Hyperkalemia	
Creatinine rise	
Dosing	
SS-daily DS – 3 X week	
DO - 3 V MACK	
Benefit of covering Toxoplasma as well	
LICE THE ANALOGY OF HER SCHOOL OF HE SCHOOL OF HER SCHOOL OF HER SCHOOL OF HER SCHOOL OF HER SCHOOL	

Case 5	46	
65 YOF with history of heart transplant 3 months prior present She was on valganciclovir and Bactrim for prophylaxis, but po- transplant course complicated by leukopenia so Bactrim switc Dapsone a couple weeks ago.	st-	
She presents now with several days of weakness, headache a dyspnea. She has blue discoloration of her lips and nails.  O2 sat 86% on RA and 87% on 6L NC.  ABG: performed with O2 sat 99% measured  What is the most likely cause of this patients illness?  A) Toxoplasmosis	and	
B) Pneumocystis C) Drug Side Effect		
HETERA SCHOOL OF MITCHAE	© LLOS ALI Riphin Pleasured	
Dapsone	a	
<ul> <li>Second line prophylactic agent</li> <li>Not sufficient for Toxoplasma prevention— (pyrimethar added)</li> </ul>	nine	
Side Effects  Hemolytic Anemia		
<ul> <li>Methemoglobinemia (both more common in patients with G6PD deficiency)</li> </ul>		
Dosing 50-100mg daily		
THE UNIVERSITY OF THE	© LLAS A B Syddy Planeword	
Atovaquone	48	
•		
<ul> <li>Suspension with bad taste</li> <li>May be sufficient for Toxoplasma prevention</li> </ul>		
Side Effects • Diarrhea		
Breakthrough infections common if under-dosed		
Dosing 1500mg daily		
LICE DIFFERENCES TYPE  ANALYSIS OF REFERENCES  HEISEN SCHOOL OF MEDICAL	6 UAS x 18;0th Sourced	

Pentamidine	49	
Aerosolized delivery		
Not sufficient for Toxoplasma prevention		
Likely inferior for PJP prevention as compared to Bactrim and Dapsor	ne	
HEESTER SCHOOL OF MEDINE SHOOL	S. 43 fights Preserved	
72		
Case 4	50	
40 y/o female with liver transplant 9 months prior for AIH presents with dyspnea.		
Transplant course complicated by CMV syndrome at 8 months and recer elevated liver enzymes treated with increased steroids.	nt	
She has 1 week of fatigue, dry cough, and increasing dyspnea. She was admitted and quickly escalated to 6L NC.		
You are the overnight admitting team & can send one test to confirm your suspicion-		
What would you send? A) CMV QNAT		
B) Beta-D-Glucan C) Urine histoplasma antigen	19)	
D) I can't answer till I complete my med-rec		
ACTION A EMPRIOR	. i.i. fights Powered	
PJP Lab Testing	sı	
Beta D- Glucan		
Polysaccharide that is a constituent of the cell wall in most fungi. Elevated with pneumocystis (and other invasive fungi) Sensitivity & Specificity (outside of HIV) 70-80% False positives: blood transfusions, Dialysis, IVIG		
LDH Helpful in HIV, but specificity low in other IC populations		
PCR testing Our assay validated for BAL samples		
Most valuable when high pre-test probability Silver Staining		
Path testing performed on BAL samples		
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PJP Management	si			
Bactrim 15-20mg/kg (prefe	erred)			
Primaquine / Clindamycin (second line)				
Adjunctive steroids?	Adjunctive glucocorticoid therapy for Pneumocystis jirovecii pneumonia in solid organ transplant recipients: A multicenter			
	COhort, 2015–2020  Issenfal: Insure-montalism', Since Submit', Sinciparen', Sense Alliuma, ' Bachera, Alteria', Sensent M. Annealism', Stemens Montalin', Gendera Canara', Annealism', Sense Alliuma, ' Issentia Marian', Sense Annealism', Sense Annealism', Sense Annealism', Issentia Marian', Sense Annealism', Sense Annealism', Sense Annealism', Issentia Marian', Sense Annealism', Sense Annealism', Sense Annealism', Sense Annealism', Issentia Marian', Sense Annealism', Sense Anne	_		
		_		
LCS HEADYSTET OF	HEFSPER SCHOOL OF MERCHE	_		
PJP Key Points	8			
Risk defined by state of immune-suppression				
<ul><li>Lung transplant highest ri</li><li>Rejection, steroids, lymph</li></ul>	sk openia, hypogammaglobulinemia, infection			
Primary prophylaxis in all for 6-12 months     Consider extension in those with risk factors				
_	exceedingly rare with Bactrim & Dapsone			
Recognizing side effects	of Bactrim and alternative agents is important			
LICE THE UNIVERSITY OF	HETERNESCHIOL OF MEDICINE GUID A RANGE Masses			
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THE UNIVERSIT ALABAMA AT E	Y OF BIRMINGHAM.	_		
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Thank yo	ou!			
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