WHAT TO DO AFTER LIVER TRANSPLANT?

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CONFLICT OF INTEREST DISCLOSURE

Commercial or Non-Profit Interest	Relationship
None	Committee member, Chair
None	Advisory board, consultant, investigator
Gilead Abbvie Lupin Pharma	Speaker
None	Stockholder, employee
None	Advisory board, research support

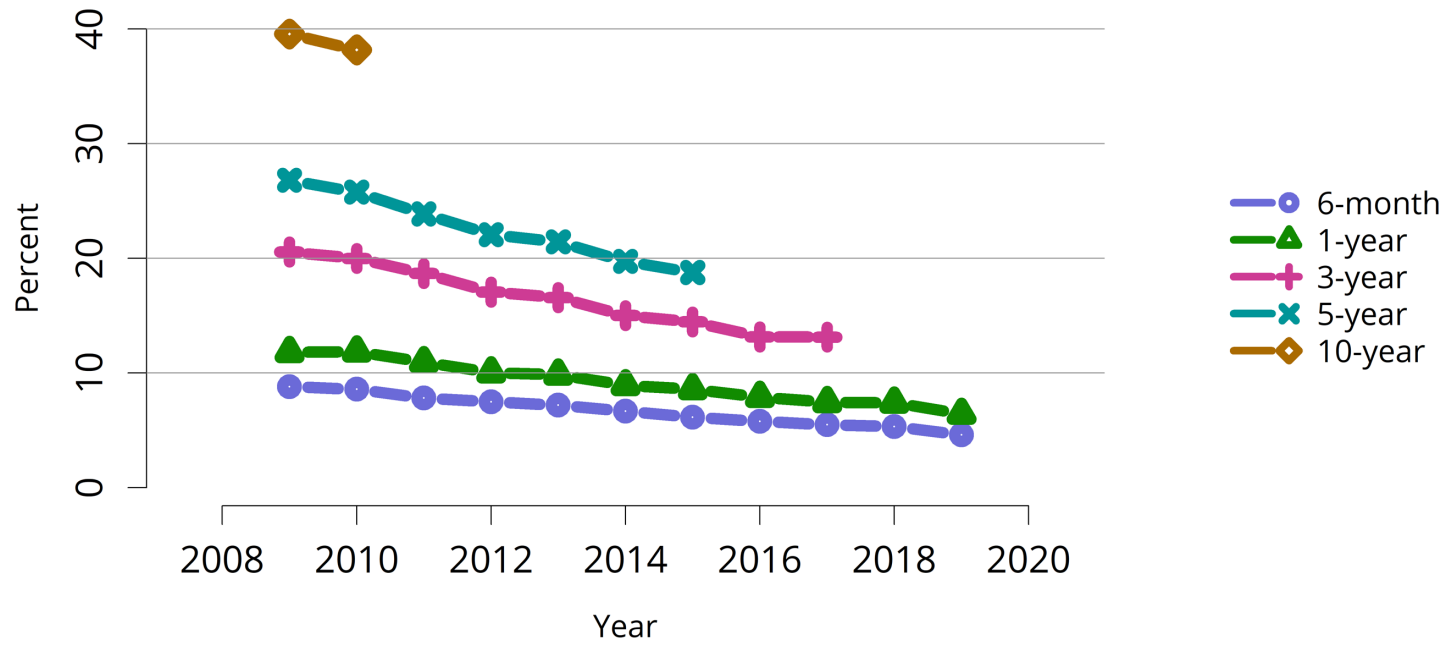
CANMEDS ROLES COVERED

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

OBJECTIVES

- Review management of immunosuppression
- Discuss surgical complications
- Review medical complications
- Discuss conception and vaccination post transplant
- Review recurrence of liver disease post transplant

POST LIVER TRANSPLANT MORTALITY



CHANGING LANDSCAPE

Recipient phenotype

- Older
- Higher frailty status
- More obesity
- Higher frequency of comorbidities (CVD, CKD)

Transplant indication

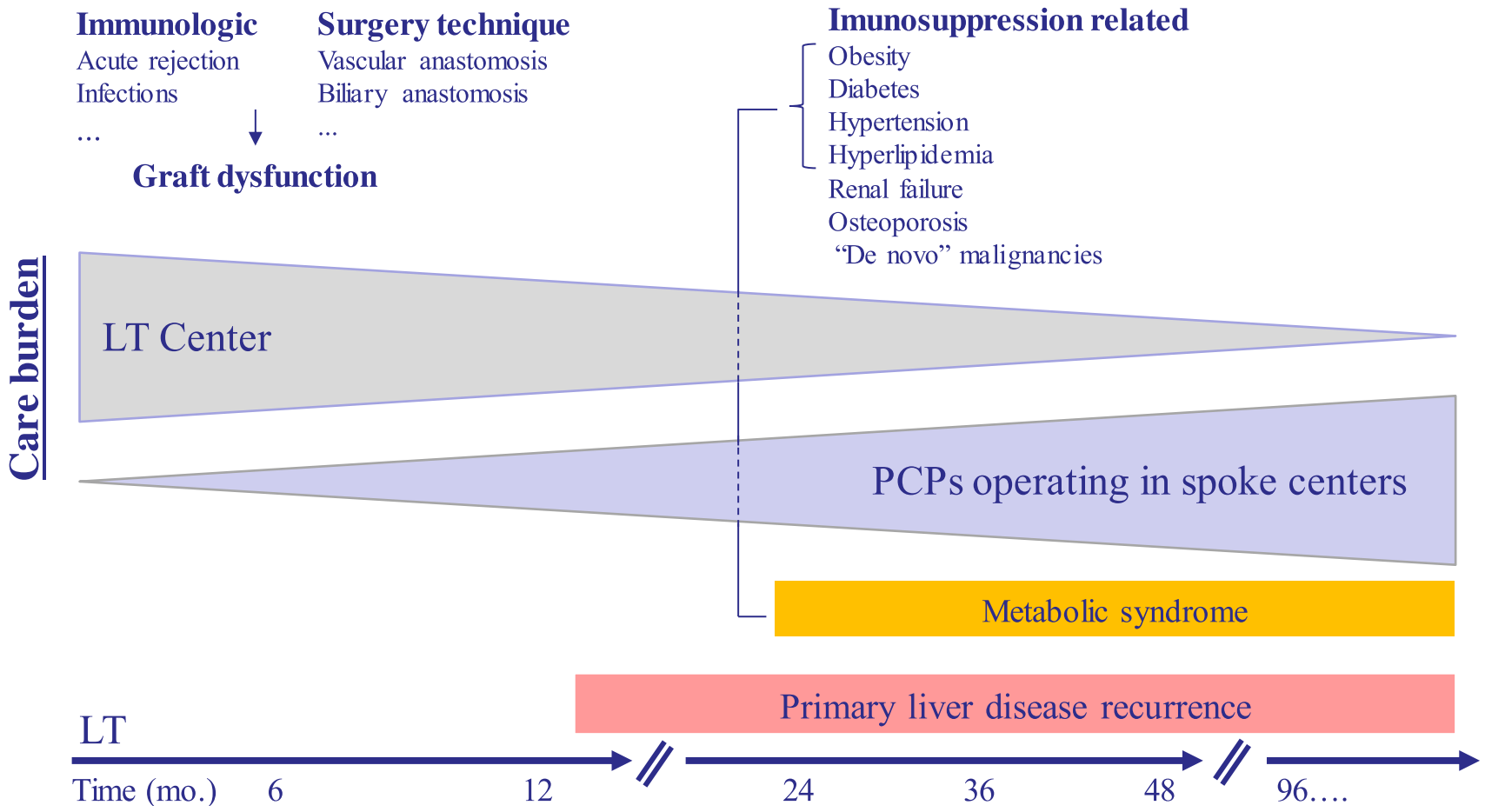
- Less HCV
- More NAFLD
- More alcohol
- Non-HCC oncologic indications

Disease severity

- Higher acuity
- Higher MELD score
- More ACLF and AH
- Expanded HCC

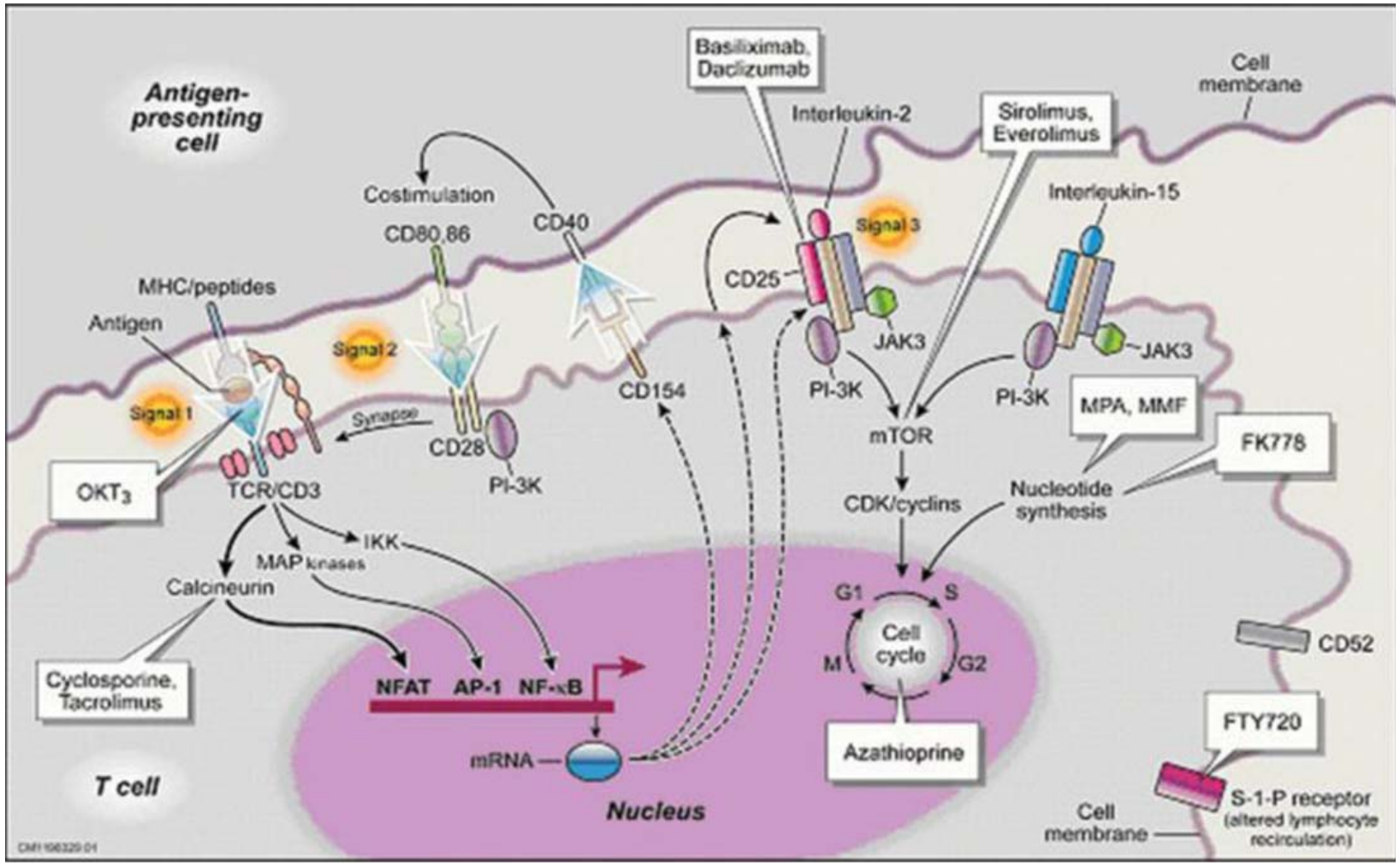
Terrault et al. Clin Gastroenterol Hepatol 2023; S1542.

POST LIVER TRANSPLANT MANAGEMENT



Toniutto et al. Am J Med 2022; 135: 157-66.

IMMUNOSUPPRESSION MECHANISM OF ACTION



Mehta et al. Clin Liver Dis 2013; 2: 188-91.

IMMUNOSUPPRESSION MANAGEMENT

Name	0-4 months	4–12 months	1 year and beyond
Tacrolimus trough (ng/mL)	7–10	4–7	4–6
Cyclosporine trough (ng/mL)	200–250	150–200	50–100
Prednisone	Tapering dose	Off	Off
Mycophenolate mofetil	1000 mg BID	Off	Off
Sirolimus (ng/mL)	10–14	8–14	8–12
Everolimus (ng/mL)	4–8	4–8	4–8

Chascsa et al. Am J Gastroenterol 2018; 113: 819-28.

IMMUNOSUPPRESSION COMPLICATIONS

SIDE EFFECT	CORTICOSTEROIDS	CNIs	mTOR INHIBITORS	MYCOPHENOLATE MOFETIL
Kidney injury	-	+++	+ (proteinuria)	-
Bone disease	+++	-	-	-
Gastrointestinal	+/-	-	-	+
Bone marrow suppression	-	-	-	+
Pulmonary fibrosis	-	-	+	-
Hypercholesterolemia	+	+	+++	-
Diabetes	++	+ (tacrolimus)	-	-
Hypertension	+	++	+	-

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Lucey et al. Liver transpl 2013; 19: 3-26.

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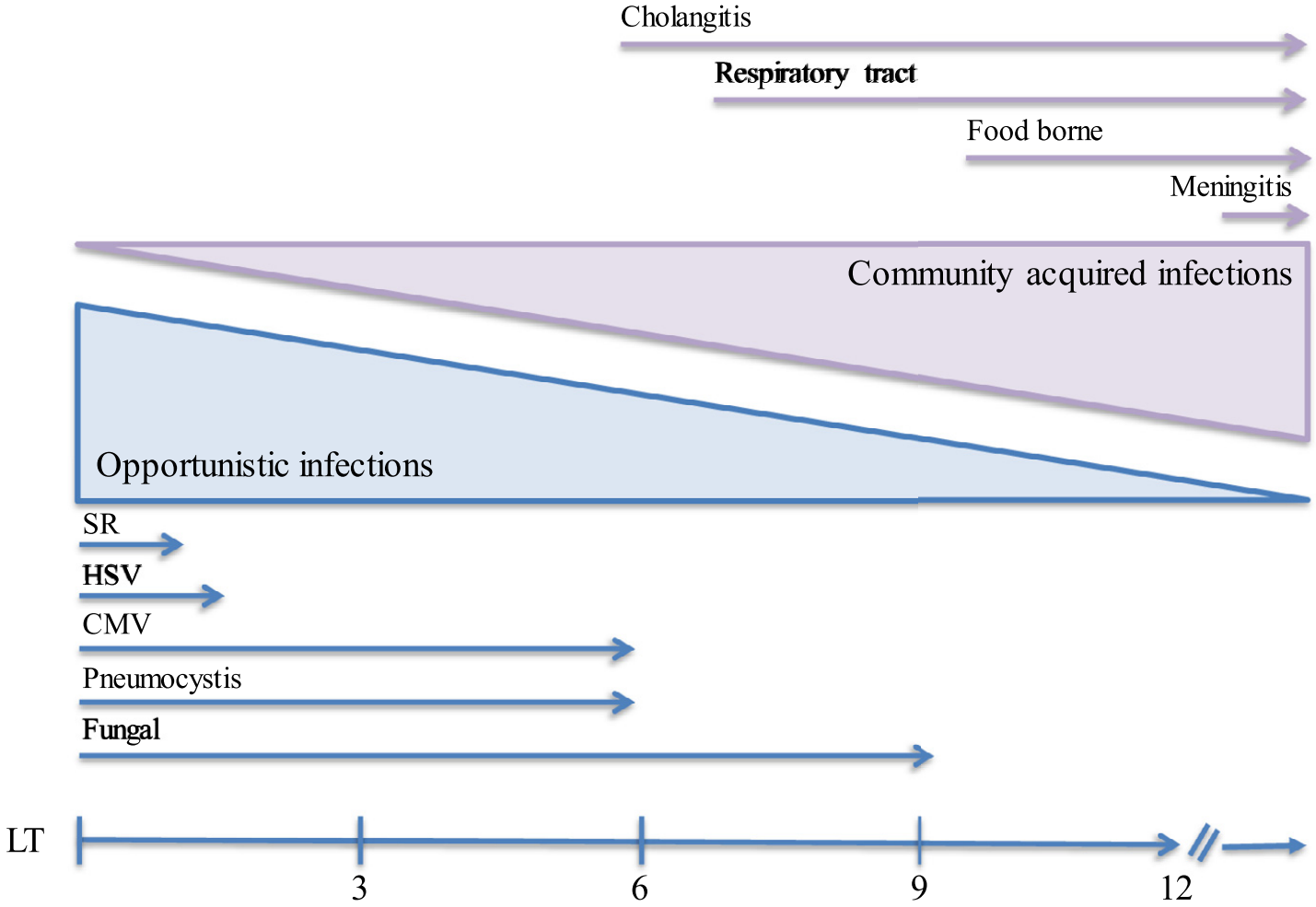
POST LIVER TRANSPLANT INFECTIONS



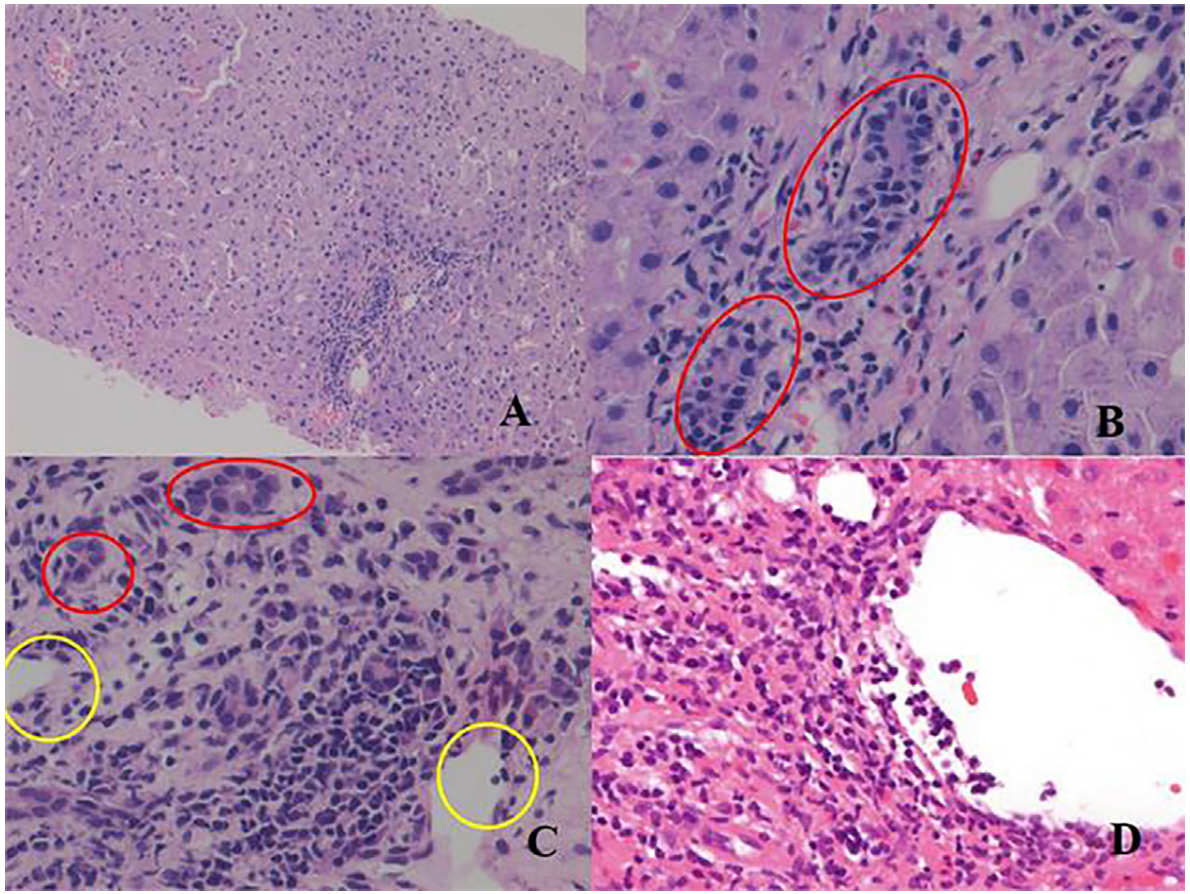
Toniutto et al. Am J Med 2022; 135: 157-66.

POST LIVER TRANSPLANT PROPHYLAXIS

ORGANISM	AGENT/DOSAGE	DURATION	COMMENTS
CMV			
Donor-positive/ recipient-negative	Valganciclovir (900 mg/day) or intravenous ganciclovir (5 mg/kg/day)	3-6 months	Valganciclovir is not FDA-approved for LT. Prolonged-duration regimens are effective in kidney transplantation.
Recipient-positive	Valganciclovir (900 mg/day), intravenous ganciclovir, or weekly CMV viral load monitoring and antiviral initiation when viremia is identified	3 months	Valganciclovir is not FDA-approved for LT.
Fungi	Fluconazole (100-400 mg daily), itraconazole (200 mg twice daily), caspofungin (50 mg daily), or liposomal amphotericin (1 mg/kg/day)	4-6 weeks? (optimal duration unknown)	Reserve for high-risk individuals (pretransplant fungal colonization, renal replacement therapy, massive transfusion, choledochojejunostomy, reoperation, retransplantation, or hepatic iron overload).
P. jirovecii (P. carinii)	Trimethoprim sulfamethoxazole (single strength daily or double strength 3 times per week), dapsone (100 mg daily), or atovaquone (1500 mg daily)	6-12 months (optimal duration unknown)	A longer duration of therapy should be considered for patients on augmented immunosuppression. Lifelong therapy should be considered for HIV-infected recipients.

Lucey et al. Liver transpl 2013; 19: 3-26.

ACUTE CELLULAR REJECTION



Treatment

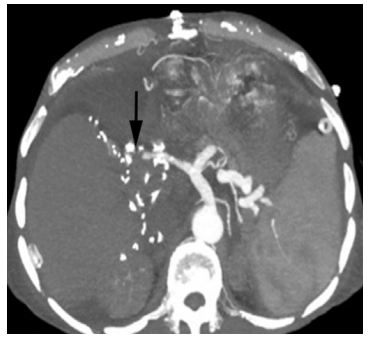
-Escalate immunosuppression

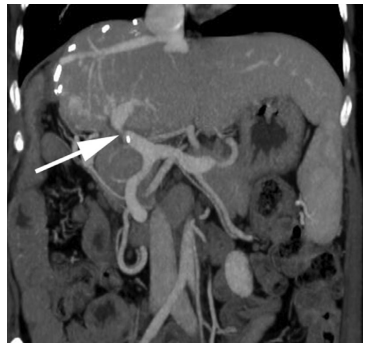
-High dose steroids

-Failures: anti-thymocyte globulin, anti-IL2 agents, etc.

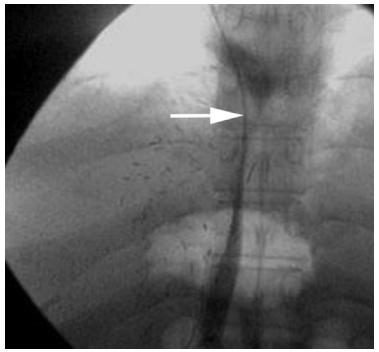
Choudhary et al. J Clin Exp Hepatol 2017; 7: 358-66.

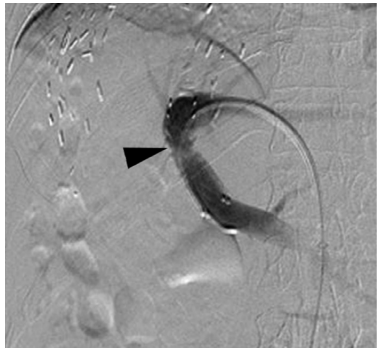
VASCULAR COMPLICATIONS





Vascular complications	Treatment options
Hepatic artery thrombosis (HAT)	Early (within 7 days) HAT – retransplantation/surgical revascularisation > endovascular management. Early (after 7 days), and Late symptomatic HAT – Endovascular management is preferred.
Hepatic artery stenosis (HAS)	Early HAS - surgical revascularisation > endovascular management. Late HAS - Endovascular management is preferred.
Hepatic artery pseudoaneurysm	Endovascular management is preferred
Hepatic artery rupture	Endovascular management/surgery
Portal vein thrombosis (PVT)	Early PVT (within 3 days) – surgical revision/ retransplantation > endovascular management. Early PVT (after 3 days), and Late symptomatic PVT - endovascular management is preferred.
Portal vein stenosis (PVS)	Asymptomatic PVS – managed conservatively with or without systemic anticoagulation. Symptomatic or tight PVS - endovascular management is preferred.
Portal vein steal syndrome	Prevention - In patients with large portosystemic shunt, or small shunt with reduced portal blood flow/pressure or portal vein stenosis in preoperative CT – shunt ligation during surgery is preferred to prevent portal vein steal syndrome. Management – Endovascular or percutaneous obliteration of shunt is preferred.
Hepatic vein, and IVC obstruction	Endovascular management is preferred.
Splenic steal syndrome or portal hyper perfusion syndrome	Endovascular management is preferred.





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Kubihal et al. J Clin Exp Hepatol 2023; 13: 854-68.

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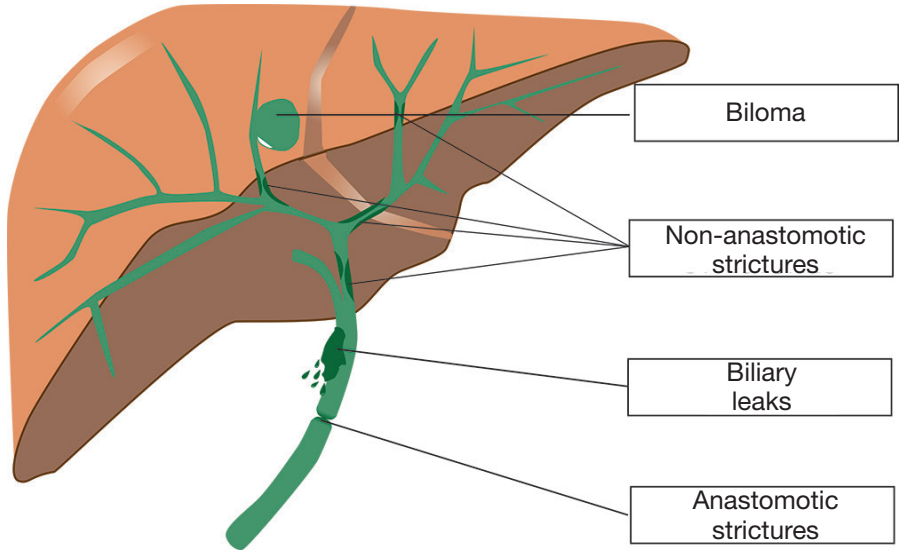
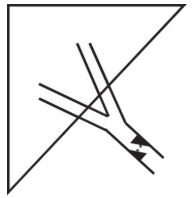
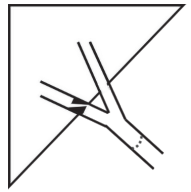
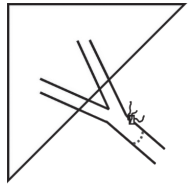
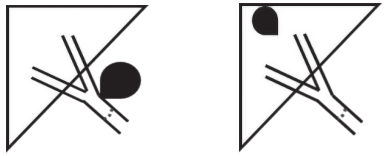
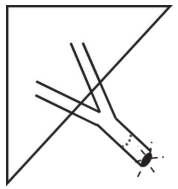
BILIARY COMPLICATIONS



Complications	Location	Incidence rate	Time of incidence
Anastomotic stricture		4–9%	Distinguished in early and late. Mostly in the first year after OLT, but even after more than 10 years
Non-anastomotic stricture		2–20%	Early (in the first year): ischemic. Late (after the first year): immunomodulation
Biliary leak		1–25%	Early (within 3 months): local ischemia or surgical complication. Late: removal of the T-tube
Biloma	 Extrahepatic Intrahepatic		Late
Sphincter of Oddi disfunction		2–5%	Median of 35 weeks (principally caused by operative denervation of the sphincter)

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Magro et al. Hepatobiliary Surg Nutr 2021; 10: 76-92.

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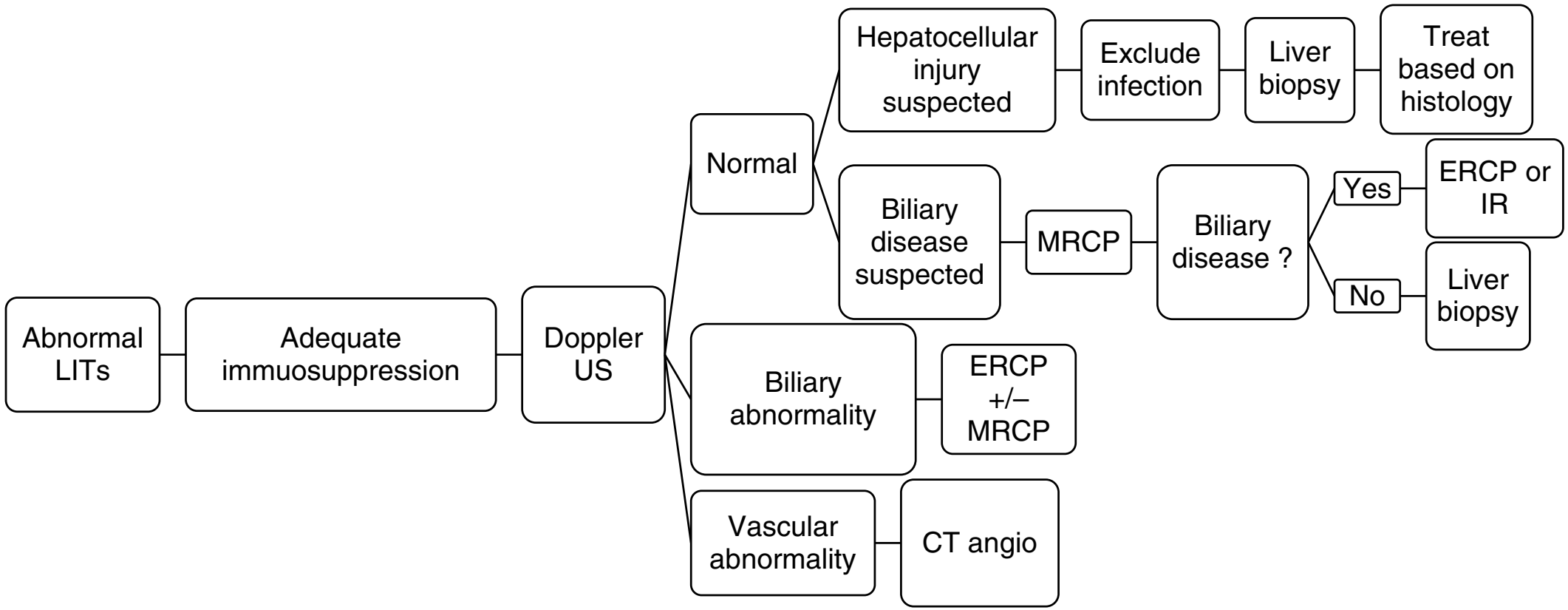
EVALUATION OF ELEVATED LIVER ENZYMES



Chascsa et al. Am J Gastroenterol 2018; 113: 819-28.

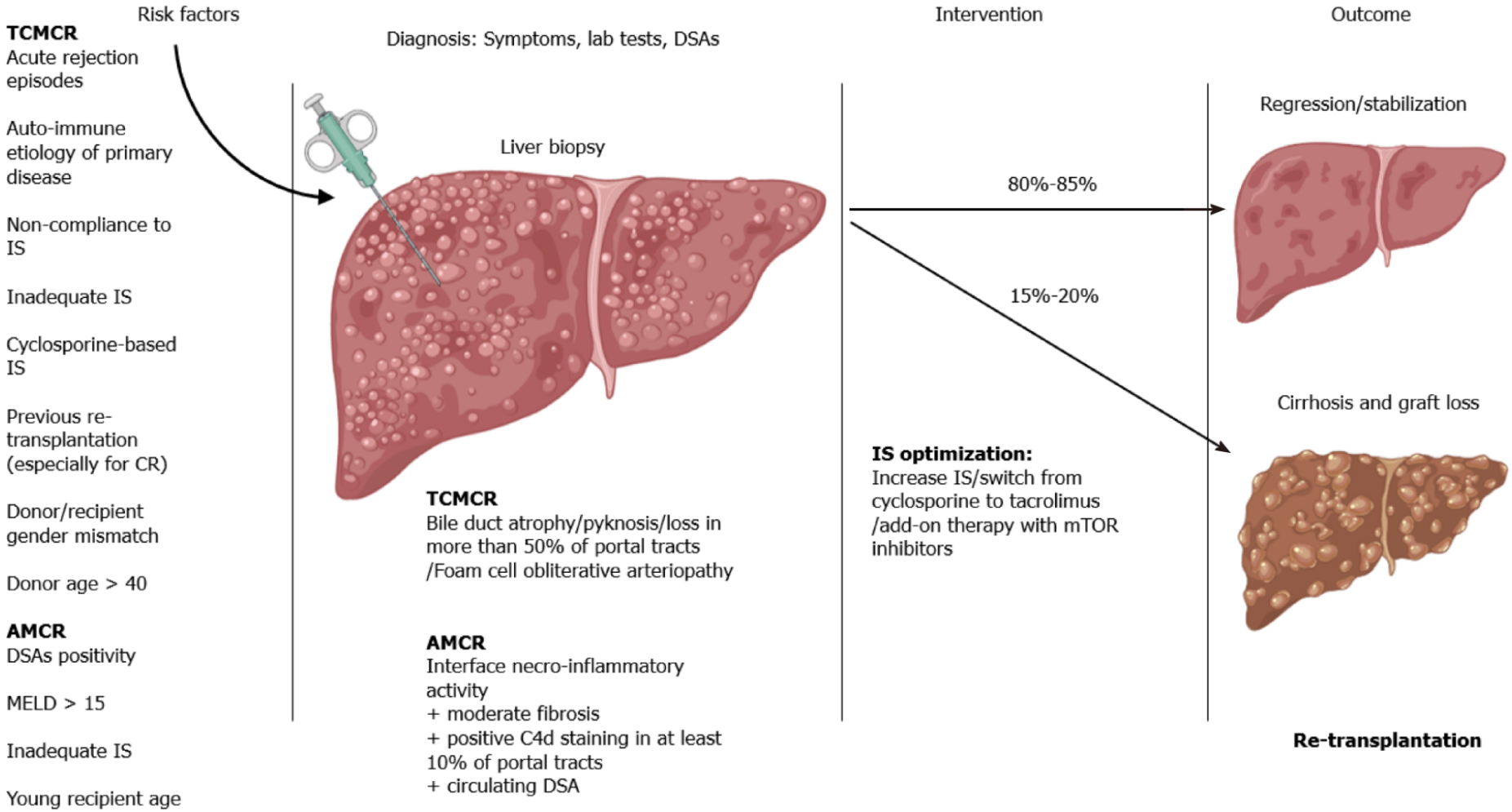
OAG GAMIFICATION

GAME CODE: **SLUSH**

LONG TERM COMPLICATIONS

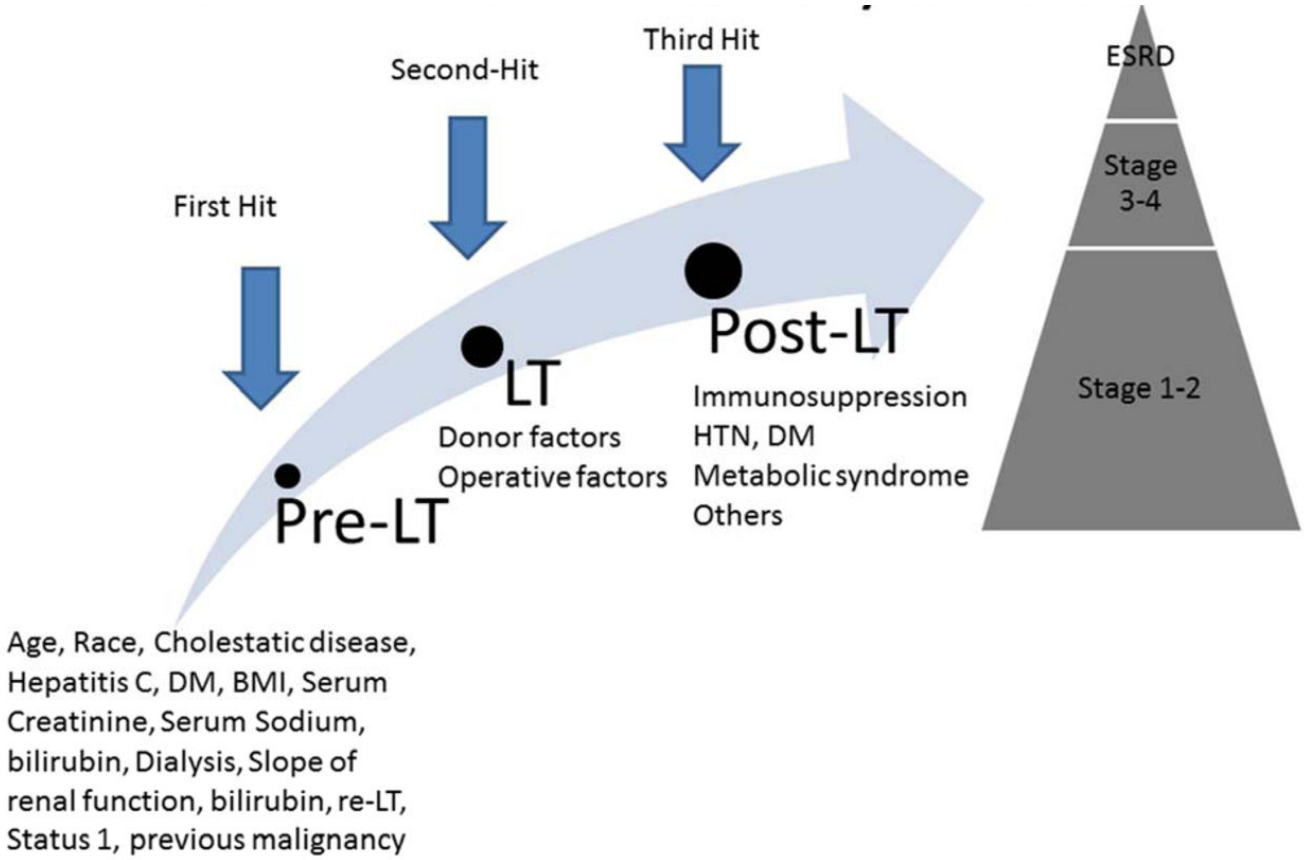
-Chronic Rejection
-Chronic Kidney Disease
-Hypertension
-Diabetes
-Dyslipidemia
-Obesity
-Cardiac Disease
-Bone Disease
-Malignancy

CHRONIC REJECTION



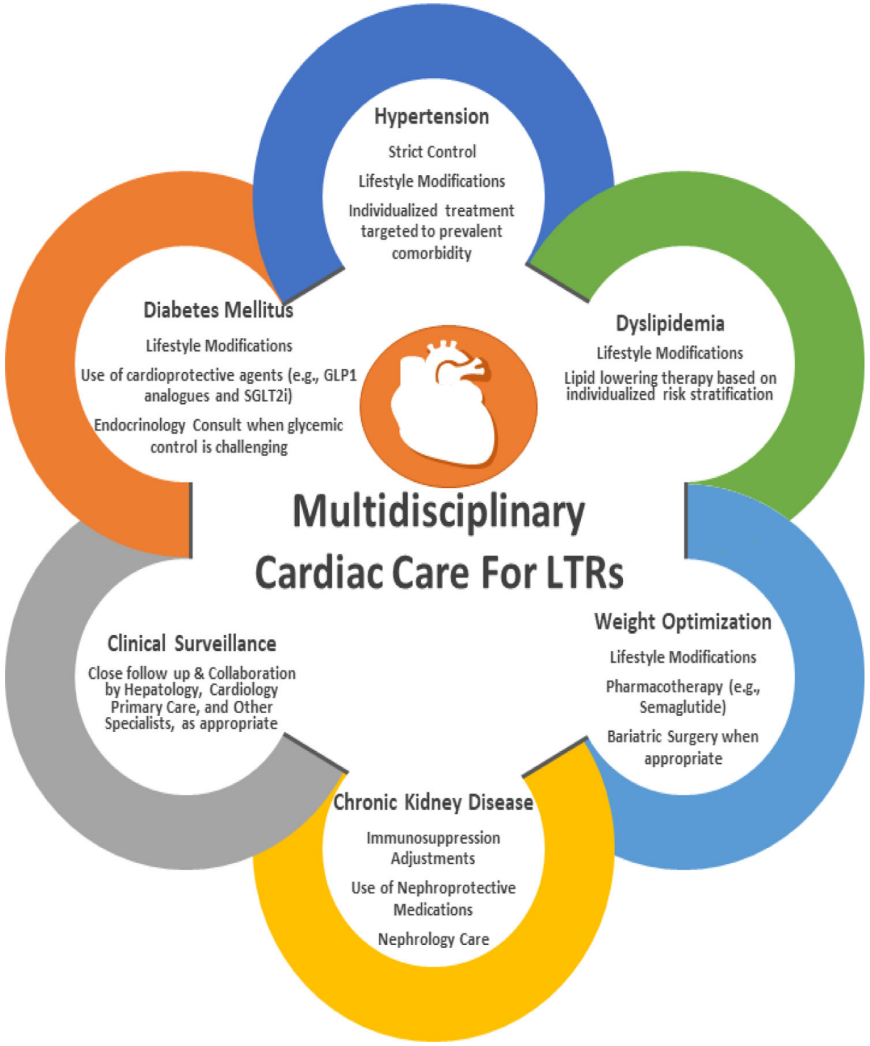
Angelico et al. World J Gastroenterol 2021; 27: 7771-83.

CHRONIC KIDNEY DISEASE



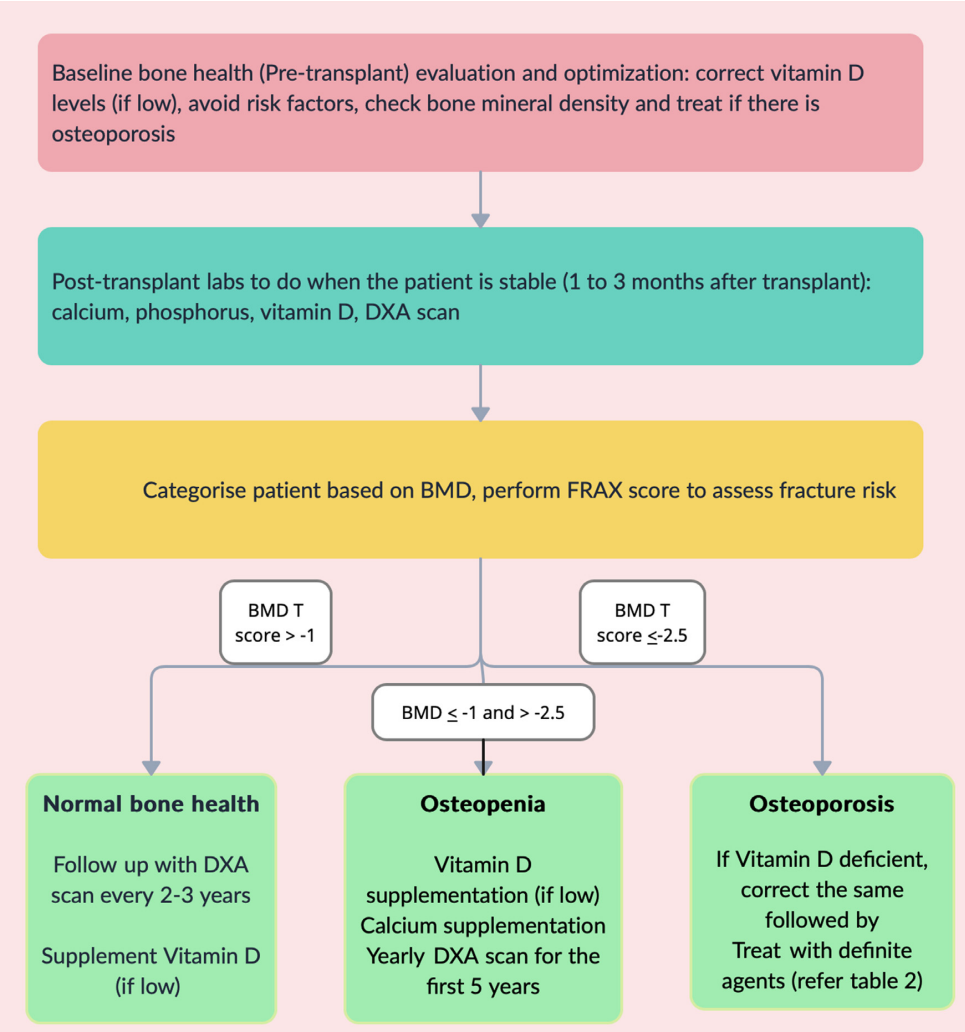
Sharma et al. Adv Chronic Kidney Dis 2015; 22: 404-11.

METABOLIC SYNDROME AND CARDIAC DISEASE



Izzy et al. Am J Transplant 2022; 22: 2740-58.

BONE DISEASE



Kumar et al. J Clin Exp Hepatol 2023; 13: 1130-39.

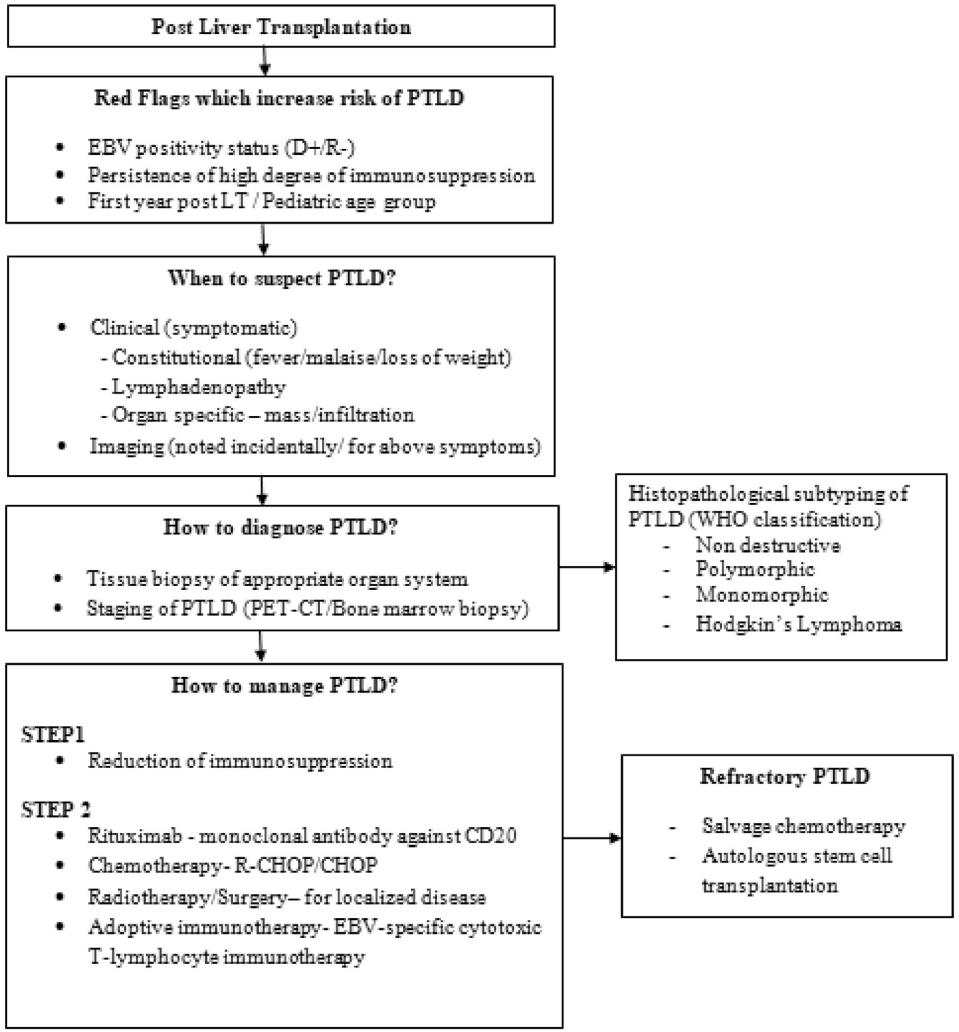
POST LIVER TRANSPLANT MALIGNANCIES

Cancer	Incidence %	Standardized incidence ratio	Screening[a]
Skin	3.3–8	13.9	Annual skin exam
Lung	0.9	13.77	Annual chest radiograph
Liver	0.5	77.94	CT or MRI first 2 years post LT at 6–12 month intervals, then annual liver ultrasound
Colorectal	0.4	7.61	Screening colonoscopy every 5–10 years Annual colonoscopy if PSC and IBD with chromoendoscopy or random biopsies
Prostate	0.4	2.34	Yearly PSA and digital rectal examination
Breast	0.3	4.00	Yearly mammogram
Head and Neck	0.3	19.29–61.59	Panorex in smokers or those with alcohol-related liver disease
Pancreas	0.1	12.08	No specific guideline PMNs managed as per non-LT
Renal	0.1	8.71	Urinalysis
Esophagus	0.1	22.69	No specific guideline
Stomach	0.07	10.90	No specific guideline
Small Intestine	0.03	14.44	No specific guideline
PTLD/lymphoma	1.2	52.90	No specific guideline

[a]There is significant practice variation based on LT center.
CT computed tomography, *MRI* magnetic resonance imaging, *LT* liver transplantation, *PSA* prostate-specific antigen, *PSC* primary sclerosing cholangitis, *IBD* inflammatory bowel disease, *PTLD* post-transplant lymphoproliferative disorder, *IPMN* intraductal papillary mucinous neoplasm

Chascsa et al. Am J Gastroenterol 2018; 113: 819-28.

PTLD



Janeela et al. J Clin Exp Hepatol 2024; 14: 101286.

VACCINATION POST LIVER TRANSPLANT

Hepatitis B	All patients should receive: - 2-dose Heplisav-B 4 weeks apart, or - 3-dose Engerix-B, Recombivax-HB or Twinrix at 0, 1 and 6 months
Hepatitis A	All patients in Europe and United States should receive: - 2 doses of Havrix 6 to 12 months apart, or - Vaqta 6 to 18 months apart, or - 3 doses of Twinrix at 0, 1 and 6 months
Pneumococcal	All patients should receive 1 dose of PCV13 followed by 3 doses of PPSV23 at: - ≥8 weeks after PCV13, - ≥5 years after the previous, - when they turn 65 years (≥5 years apart from the second PPSV23 dose)
Influenza inactivated	Adult patients should receive 1 dose annually
Zoster live attenuated (Zostavax)	Not recommended
Zoster recombinant (Shingrix)	Not recommended. If given, it should be administered before LT
Tetanus, diphtheria and pertussis	All patients should receive 1 dose of Tdap, then Td or Tdap booster every 10 years
Measles, mumps and rubella	Not recommended. It should be given before LT
Human papillomavirus	All patients should receive 3 doses through age 26
Meningococcal ACWY and B	Recommended for adults with an additional risk factor/indication, *e.g.* anatomical or functional asplenia, haematopoietic stem cell transplant or other additional factors
Haemophilus influenzae	Recommended for adults with an additional risk factor/indication, *e.g.* anatomical or functional asplenia, haematopoietic stem cell transplant or other additional factors
COVID-19 vaccine	Adult patients should receive: - 3 doses of Pfizer-BioNTech mRNA, or - 3 doses of Moderna mRNA, or - 2 doses of Novavax Adjuvanted, or - 1 dose of Janssen Adenoviral vector followed by mRNA vaccine; all followed by booster dose of mRNA vaccines ≥2 months after primary series

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Ballester et al. JHEP Reports 2023; https://doi.org/10.1016/j.jhepr.2023.100776.

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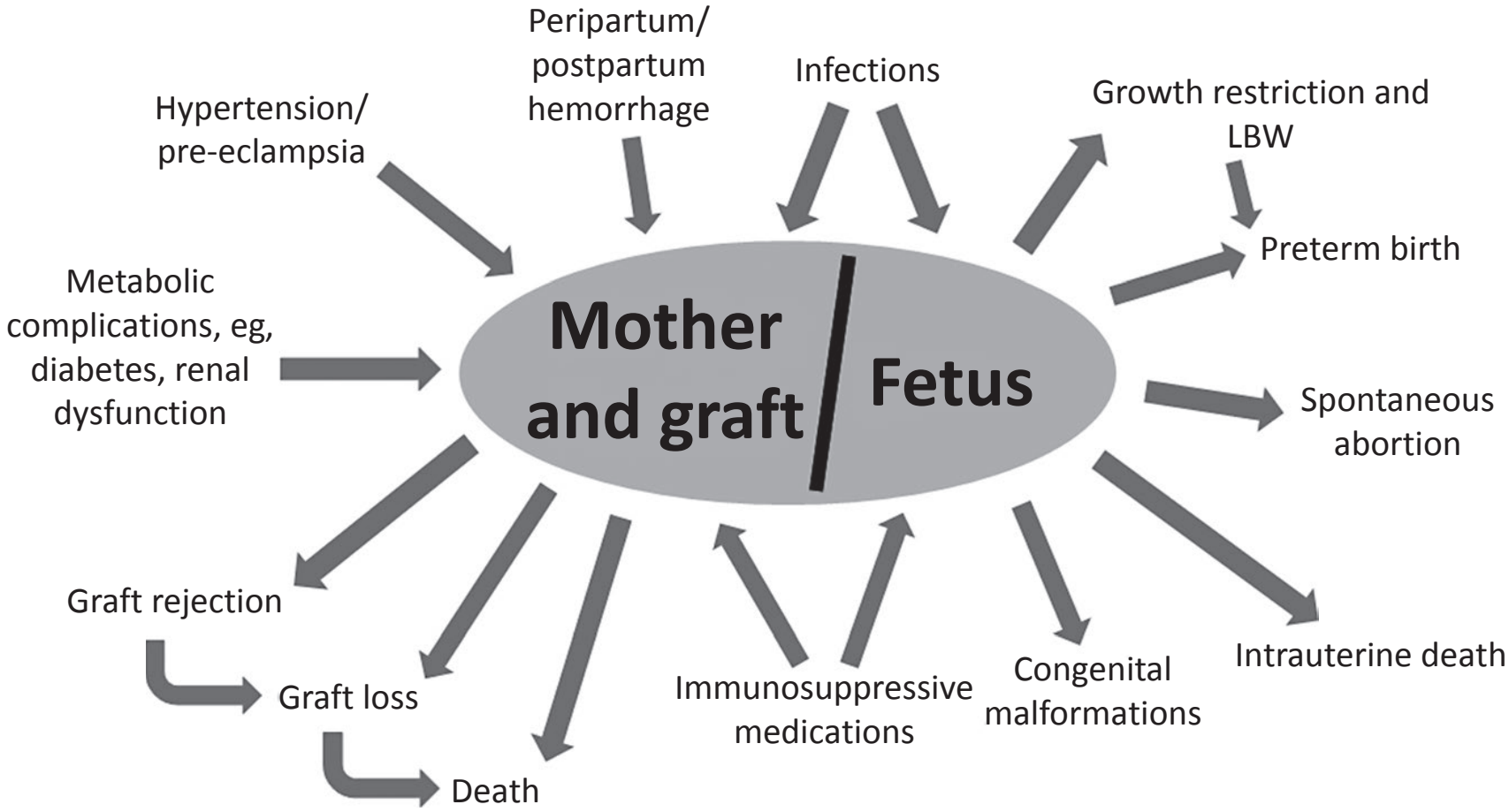
COVID TREATMENT POST LIVER TRANSPLANT

Therapy	Route	Indications	Comments
Sotrovimab	IV or IM	Early outpatient treatment	Effective against BA.1, BA.1.1; reduced activity vs BA.2
Bebtilovimab	IV	Early outpatient treatment	Effective against BA.1, BA.1.1, BA.2
Nirmatrelvir/ritonavir	Oral	Early outpatient treatment	Potentially severe drug-drug interactions
Molnupiravir	Oral	Early outpatient treatment	Not for use in pregnancy
Remdesivir (3-d outpatient course)	IV	Early outpatient treatment	Logistics may be challenging
Convalescent plasma	IV		Early use of high-titer plasma showed benefit
Tixagevimab/cilgavimab	IM	Pre-exposure prophylaxis	More active against BA.2 than BA.1 or BA.1.1

Avery. Transplantation 2022; 106: 1528-37.

LIVER TRANSPLANT AND PREGNANCY



Rahim et al. Liver Transpl 2020; 26: 564-81.

IMMUNOSUPPRESSION AND PREGNANCY

Medication	Pregnancy	Breastfeeding	Comments
Azathioprine	OK	OK	
Cyclosporine	OK	OK	
Everolimus	Not OK	Not OK	Associated with low birth weight and preterm birth
Mycophenolic acid products	Not OK	Not OK	High risk of miscarriage and birth defects. Stop using 6 wk before conception
Prednisone	OK	OK	
Sirolimus	Not OK	Not OK	Associated with low birth weight
Tacrolimus	OK	OK	Associated with high blood pressure, pre-eclampsia, and preterm birth

Levy et al. Clin Liver Dis 2023; 21: 19-35.

RECURRENT LIVER DISEASE

Etiology of Liver Disease	Subtype	5-year recurrence rate
Hepatitis B[15] (with HBIG and nucleotide analogs)	Positive HBV DNA	0%–20%
Hepatitis C[21] (before DAA)	Histologic recurrence	95%
	Cirrhosis	20%–40%
	Fibrosing cholestatic hepatitis	2%–5%
Hepatitis C[25] (after DAA)	Virologic relapse	0.8%
	Fibrosing cholestatic hepatitis	0.5%
Alcohol[6]	Any alcohol use	42%
	Binge-pattern alcohol use	26%
	Frequent alcohol use (≥2 drinks/day)	20%
	Alcohol-associated cirrhosis in patients with severe relapse	35.2%
NAFLD[11]	Recurrent	60%
	De novo	35%
Autoimmune hepatitis		35%–65%
PBC[34]		20%
PSC[31]		20%
Hepatocellular carcinoma[43]		11%–18%

Goel et al. Liver Transplantation 2022; 00: 1-9.

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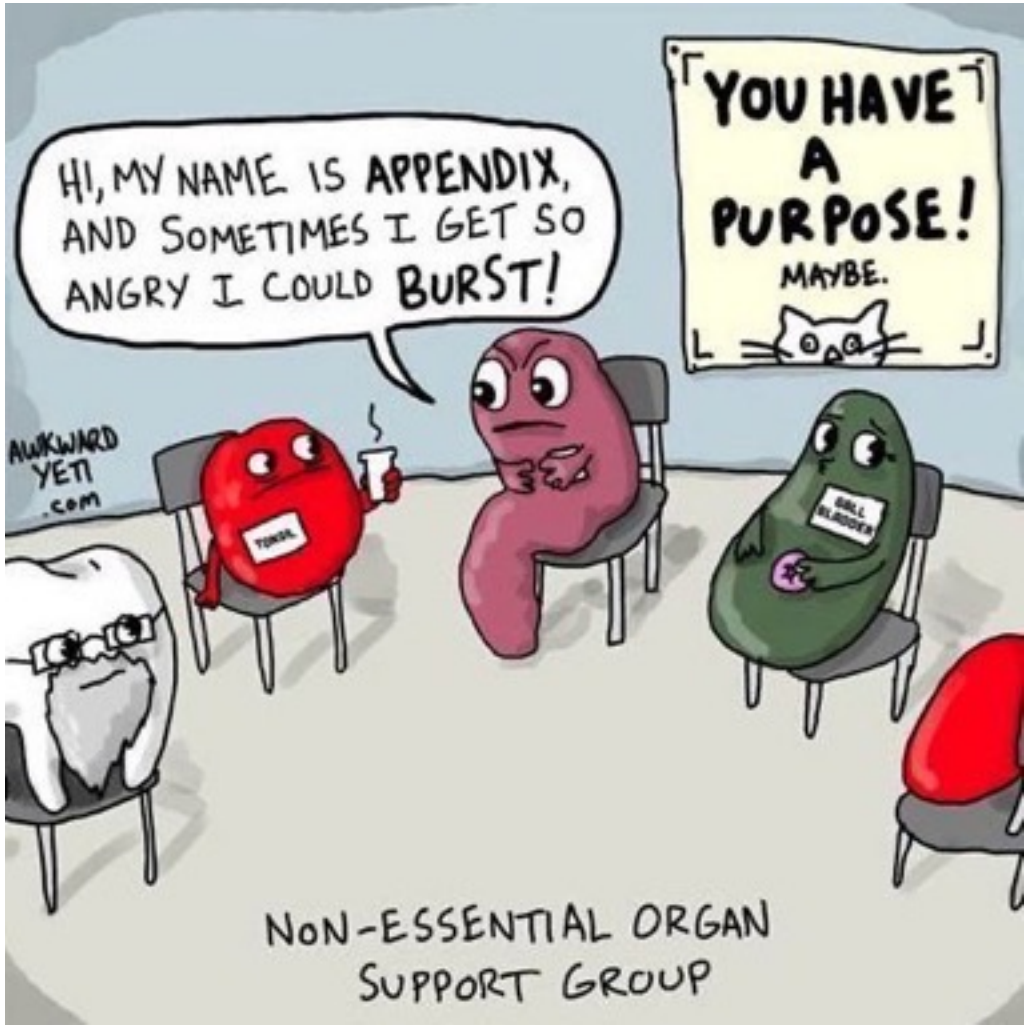
THANK YOU



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