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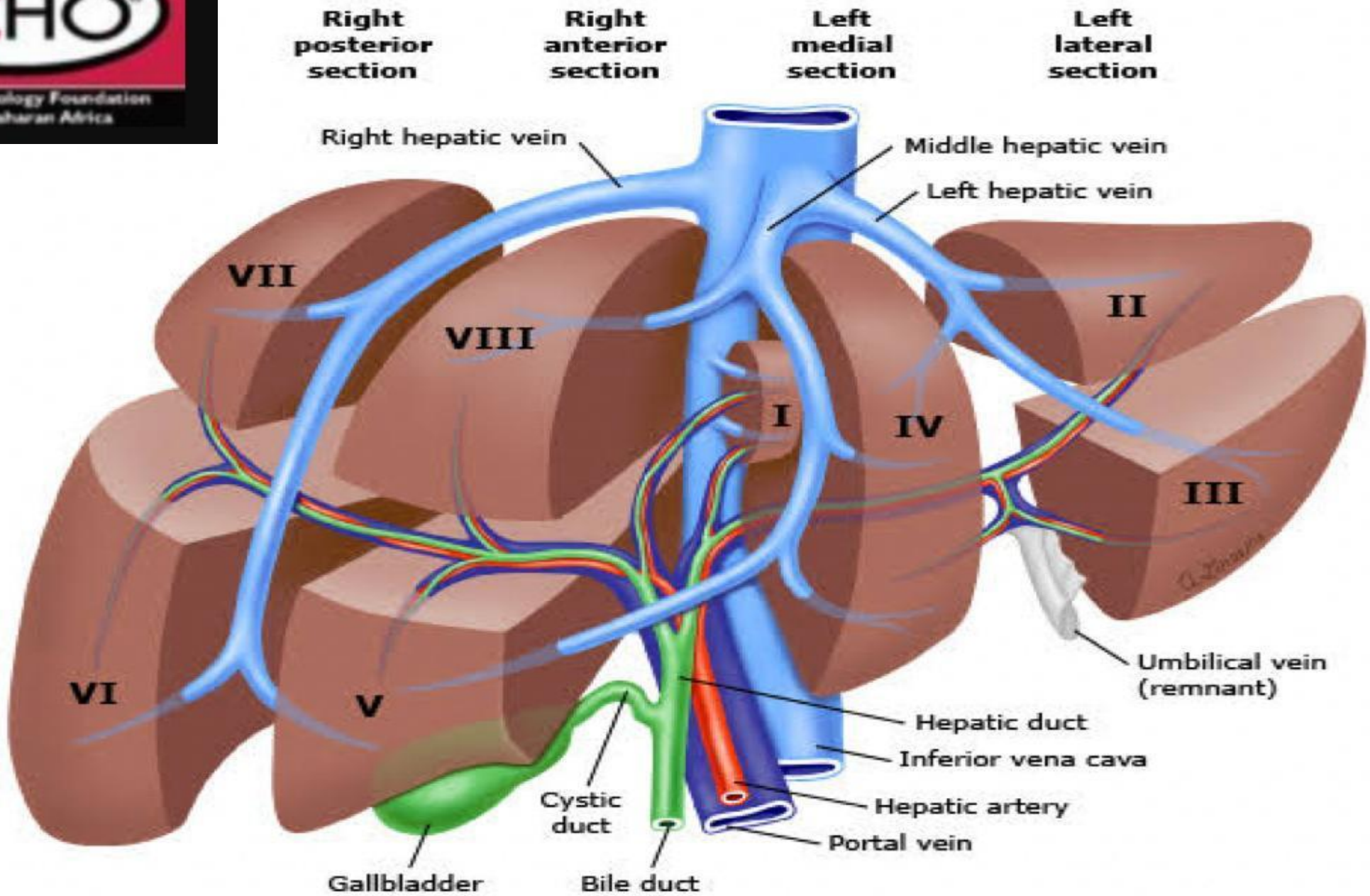
LIVER TRANSPLANTATION ASSESMENT INDICATION AND POST OPERATIVE CARE



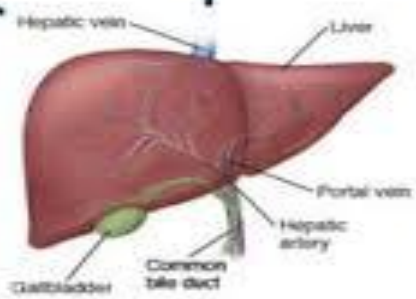
Functions of the Liver

Detoxification:
- Drugs/Alcohol
- Fatty acids
- Steroid hormones
- Ammonia → Urea
- Environmental toxins/allergens

Production of Cholesterol:
- Precursor to sex hormones, Vitamin D

Storage of Micronutrients:
- Minerals: Copper, Zinc, Magnesium, Iron
- Vitamins: Vitamin A, D, E, K, B12

Metabolism:
- Conversion of T4 → T3
- Detoxification of fat

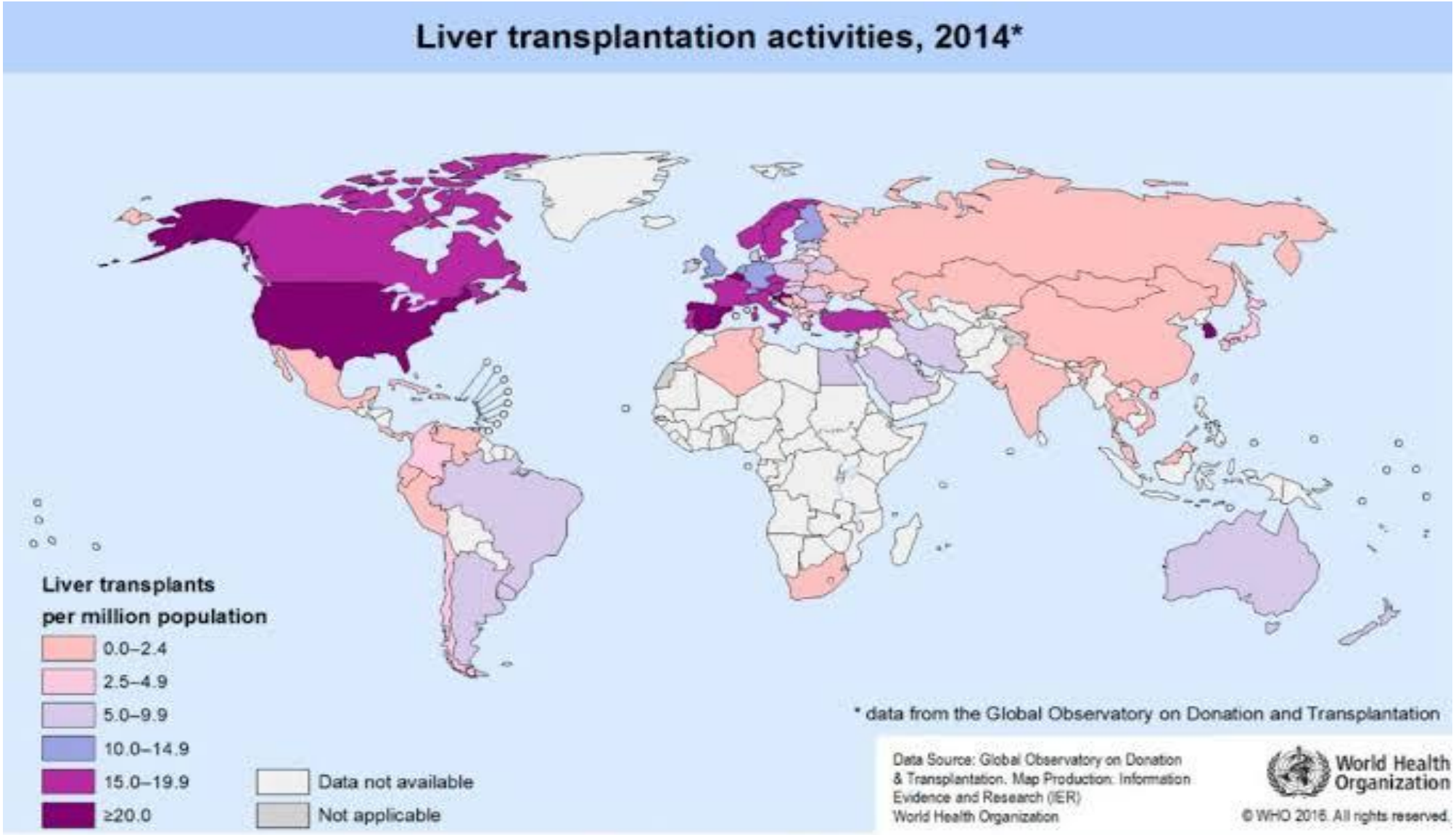


Blood Sugar Balance:
- Storage of glycogen

Immune System:
- Contains viruses and pathogens
- Maintenance of the hepatic and portal vein immune system

Production of Bile:
- Needed for digestion
- GI anti-microbial

Protein Synthesis:
- Blood clotting (prothrombin)
- Cholesterol transport (lipoproteins)
- Immune Function (globulins)
- Oncotic pressure (albumin)
- Copper bioavailability (ceruloplasmin)


Liver transplantation activities, 2014*
Liver transplants
per million population
0.0–2.4
2.5–4.9
5.0–9.9
10.0–14.9
15.0–19.9
≥20.0
Data not available
Not applicable
* data from the Global Observatory on Donation and Transplantation
Data Source: Global Observatory on Donation & Transplantation. Map Production: Information Evidence and Research (IER) World Health Organization
World Health Organization
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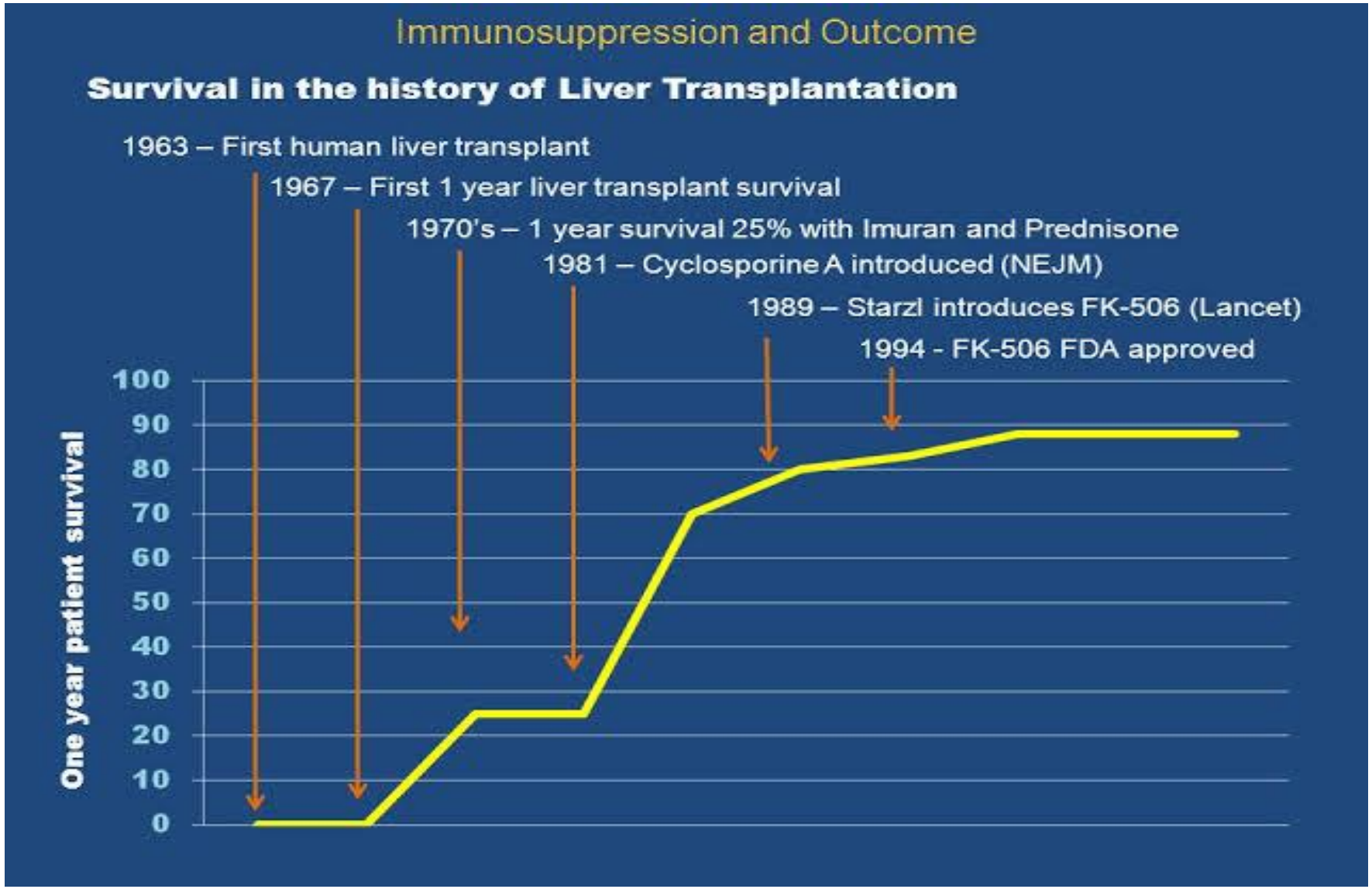

Immunosuppression and Outcome
Survival in the history of Liver Transplantation
1963 – First human liver transplant
1967 – First 1 year liver transplant survival
1970's – 1 year survival 25% with Imuran and Prednisone
1981 – Cyclosporine A introduced (NEJM)
1989 – Starzl introduces FK-506 (Lancet)
1994 - FK-506 FDA approved
One year patient survival
100
90
80
70
60
50
40
30
20
10
0

HISTORY OF LIVER TRANSPLANTATION

- Last 25 years s has improved (90- 96%)at 1 year and (70 to71%)at 10years in terms of quality of life and length of survival
- 2nd most type of solid organ transplantation
- Deceased donor or living donor
- Explanted liver are perfused and stored in cold preservation solution for 18hrs before transplantation
- Prolonged storage increase incidence of Ischaemic type biliary injury and organ non function
- Recipient hepatectomy demanding part due to portal hypertension and coagulation problems
- Anastomoses vena cava , hepatic artery , portal vein and biliary duct

Aim of liver transplantation

- Safe life
- Improve life expectancy and improve quality of life’s

Liver transplant

- Irreversible acute liver failure
- Irreversible chronic liver failure
- Improve patient and graft survival

Complications of liver transplantation

Early complication

- Primary non function 4-6% cases need re transplantation
- Vascular compromise (hepatic artery thrombosis within 2week need re transplant and portal vein thrombosis
- Infection (line sepsis, pneumonia, urinary tract infection, intra abdominal abscess)
- Bile leaks
- Bleeding

Late complication

- Biliary stricture
- Vascular stricture /thrombosis
- Opportunistic infection
- Metabolic syndrome
- Immunosuppressant side effects and toxicity
- Malignancy (skin , lymphoma)a sa A
- Recurrence of disease

Why survival rate has improved in patient and allograft

- Immunosuppressant
- Preservation solution
- Proper candidate selection
- Improvement in surgical technique and peri operative management including anaesthesia
- Early diagnosis and management of complications post liver transplant

That has led to ability to expand further indications for liver transplantation

Challenges

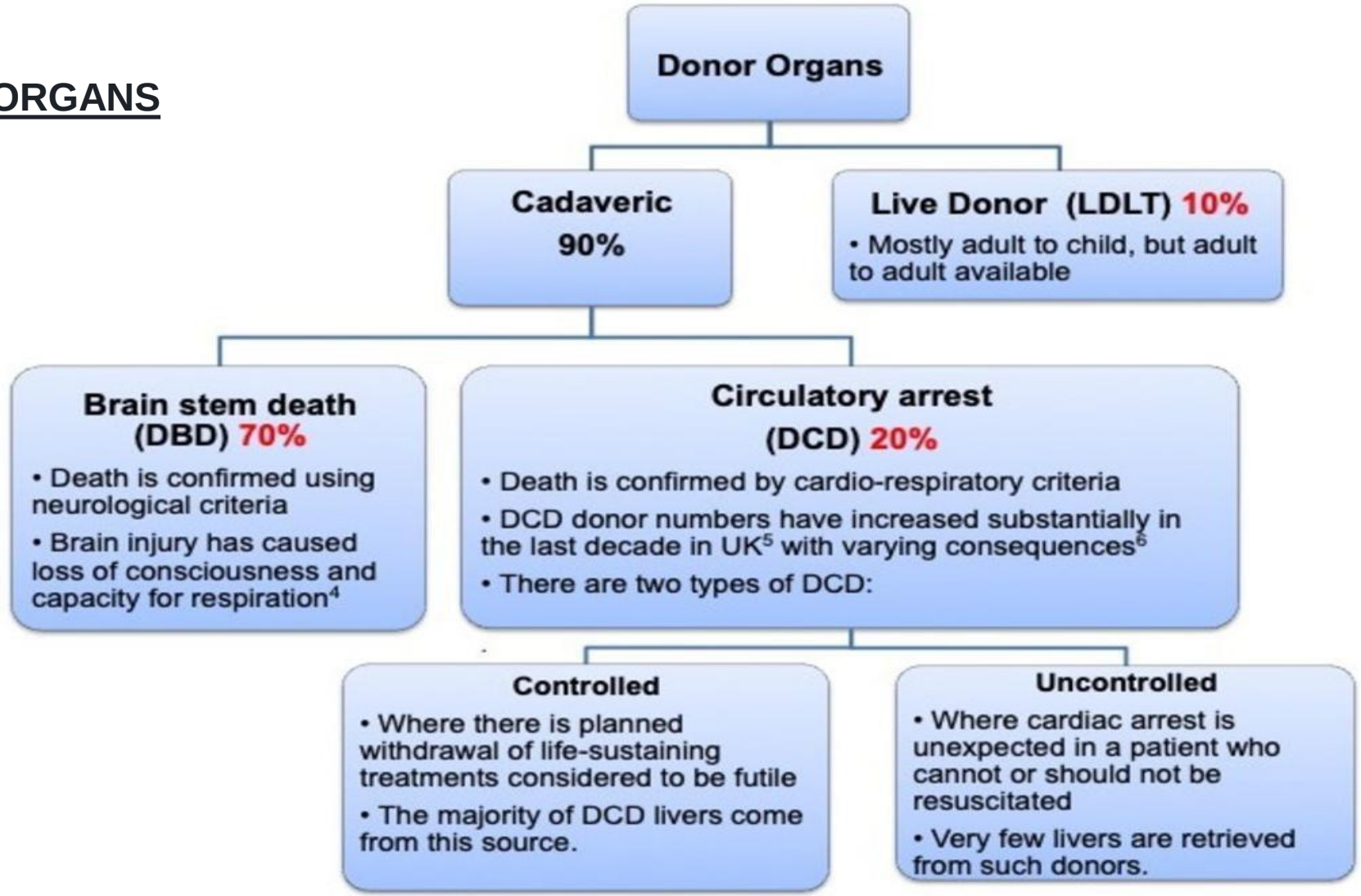
- Organ shortage / limited organ available
- Increase demand for organ transplant hence too many Patients of waiting list , some die awaiting liver

Mitigate challenges of liver transplantation

- Living donor liver transplant
- Split donor liver transplant
- Expanded criteria donor or Marginal allograft

(donor age >65 years ,hepatic steatosis >30% of liver allograft, prolonged ICU stay, use of multiple vasopressor and prolonged cold Ischaemia)

TYPES OF DONOR ORGANS



LIVING DONOR

- Asia LDLT around 90%
- Left hepatic lobe for paediatrics and right hepatic lobe for adults

Advantage of LDLT

- Graft from healthy individuals with short Ischaemic time
- Ability to schedule surgery effectively
- Decrease risk of recipient dying on waiting list

Disadvantage of LDLT

- Risk for healthy donor
- Potential risk for small for size syndrome
- Higher rate of surgical complications for both

Living donor assessment

- Psychological evaluation
- Evaluate for clinical examination (liver , renal and other disease
- Serological test(HIV , EBV , CMV , Herpes)
- Diagnostic studies to evaluate vascular and biliary anatomy of the liver (Multiphase liver CT, Dupplex Ultrasound and MRI)

Donor complication

- Excessive bleeding
- Bile leakage
- Infection
- Thromboembolic event
- Incisional hernia
- Death

DECEASED DONOR

i. Whole liver from deceased donor
ii. Split liver from deceased donor (paediatric recipient left lateral segment and adult recipient R lateral lobe)

SURGICAL CHALLENGES

- Removal of deceased liver from abdominal cavity with extensive venous collateral due to portal hypertension , remove diseases liver from recipient
- Implantation of graft and creating a vascular and biliary anastomoses

Surgery complex on debilitated recipient due advanced liver disease
Immunosuppressant

CRITERIA FOR LIVER TRANSPLANT

- Irreversible disease that would be fatal without transplantation
- No contraindications to liver transplant surgery
- Able to pass extensive transplant evaluation

LIVER ALLOCATION

- Sickest patient first priority measure by MELD score
- 20-30% of patients will die on liver waiting list and others would be too sick or just cannot make it to the waiting

Allocations depend

- Meld score
- Fraility score
- Match to donor
- Local or regional priority

MDT Multi disciplinary team

- Transplant hepatologist
- Transplant surgeon
- Cardiologist
- Nephrologist
- Pulmonologist
- Intensivist
- Psychiatrist
- Social Worker
- Dietician
- Transplant Pharmacist
- Care giver /Support personnel

INDICATION FOR LIVER TRANSPLANTATION

<u>SPECIAL CATEGORY 1 FOR LIVER TRANSPLANT(EMERGENGY)</u>

1. ALF plus encephalopathy in ICU with life expectancy <7 days without liver transplantation
2. Children < 18 years of age in ICU with acute liver failure and chronic liver failure experiencing

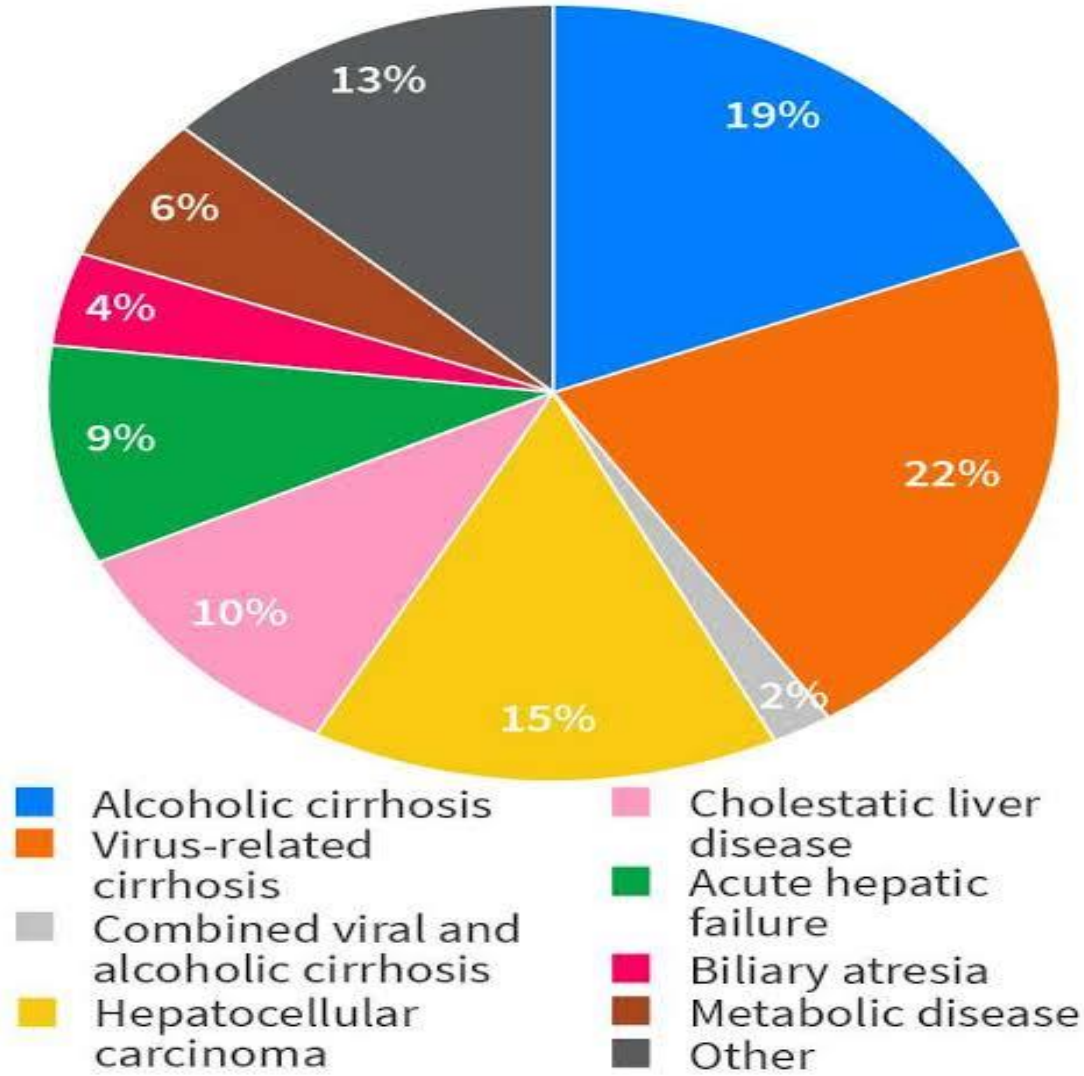
- GIT bleeding
- Uncontrolled portosystemic encephalopathy
- Hepatorenal syndrome
- Refractory ascites
- Estimated life expectancy <7days

3. primary graft failure

- Hepatic artery thrombosis

4. Fulminant Wilson disease

INDICATIONS FOR LIVER TRANSPLANTATION



Severe alcoholic hepatitis

Acute-on-chronic liver failure grade 3

New indications for liver transplantation

Colorectal liver metastases

Intrahepatic and perihilar CCA

Absolute contraindications

- Severe pulmonary hypertension (mean PAP>50mmHg
- Elevated intracranial pressure >40mmHg

Absolute contraindications
Severe cardiopulmonary disease
Extrahepatic malignancy (oncologic criteria for cure not met)
Active alcohol/substance abuse
Acute alcoholic hepatitis
Active infection/uncontrolled sepsis
Lack of psychosocial support/inability to comply with medical treatment
Brain death
Relative contraindications
Advanced age
Acquired immune deficiency syndrome
Cholangiocarcinoma
Diffuse portal vein thrombosis

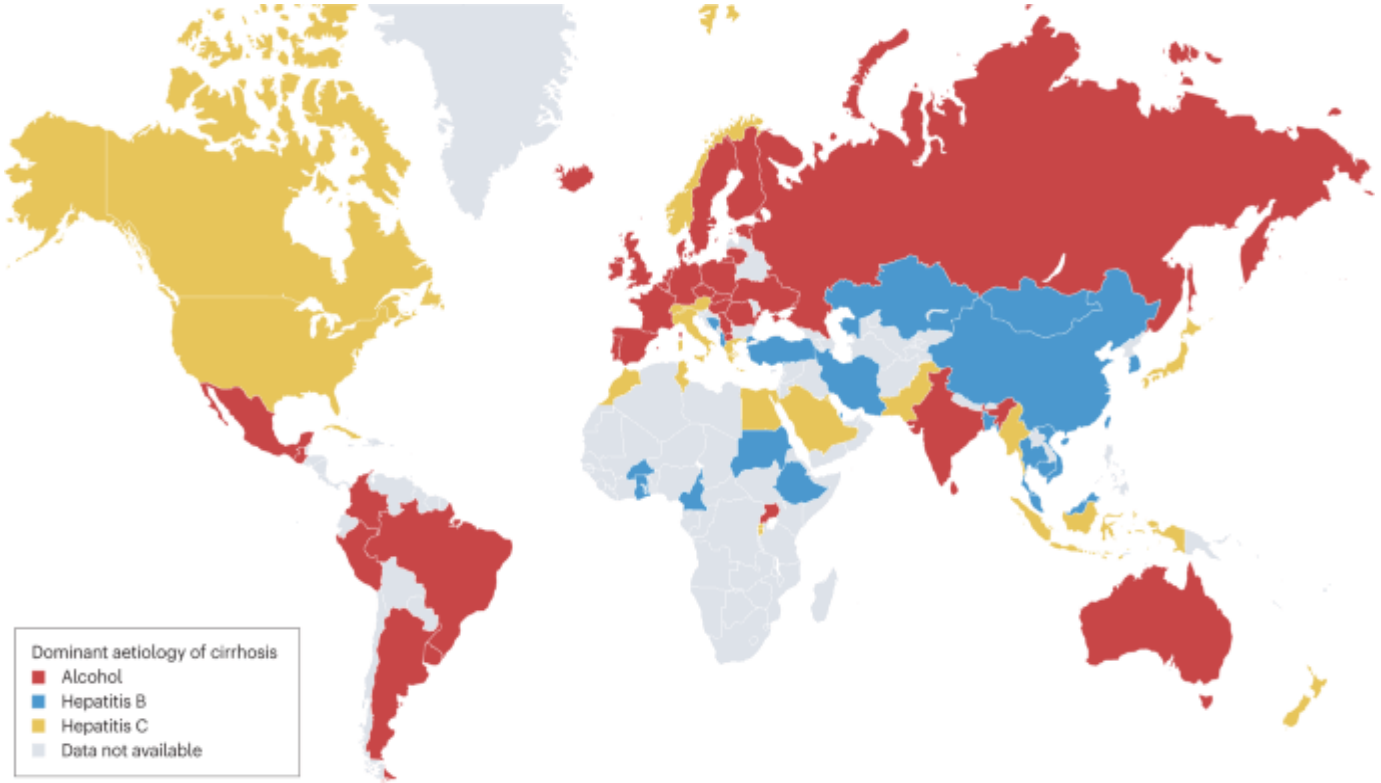
1. ESLD/Cirrhosis

- decrease survival than the rest of population
- Major complication predictor of decrease survival and prompt evaluation for liver transplantation

Causes of Cirrhosis

- Most common
- ***Chronic viral hepatitis***
  - ***HBV***
  - ***HCV***
- Alcoholic liver disease
- ***Hemochromatosis***
- ***NASH***
  - Non alcoholic steatohepatitis

- Less common causes
  - Autoimmune hepatitis
  - Primary and secondary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Medications
  - Wilson disease
  - Alpha-1 antitrypsin deficiency
  - Granulomatous liver disease
  - Polycystic liver disease
  - Right-sided heart failure
  - Veno-occlusive disease.



50% of ESLD

- Alcoholic liver disease
- Viral hepatitis
- MAFLD/NAFLD
- Autoimmune hepatitis
- Cholestatic liver disease(PSC and increase in IBD

- Liver transplant would extend life expectancy beyond natural history of underlying liver disease would predict
- Unacceptable quality of life because of liver disease and liver transplant would likely improve quality of life
- Selected if expected survival in the absence of transplant is 1year or less

TIMING OF OF LIVER TRANSPLANT IN ESLD

- Best prior to life threatening complications
- Not too early and not too late

DETERMINANTS OF LIVER TRANSPLANT

a) MELD na > 15

- Meld score ranges from 6-40 scale

(Bilirubin, INR , Creatinine and Na)

- Predict chance of dying within 3/12 without LT
- MELD 6=10% chance of death in 3/12
- MELD > 20 =25% chance of dying within 3/12
- MELD >40=90% chance of dying within 3/12
- Used for organ allocation for liver transplantation
- Development of hyponatraemia in cirrhosis is a marker of Increase waiting list mortality and high risk of neurological dysfunction post liver transplantation

Limitation of MELD score

- Creatinine (ESLD with renal failure increase LT, women at disadvantage due to low mass
- PSC

Table 2. Exceptions to MELD score.

Manifestations of cirrhosis
Refractory ascites
Recurrent gastrointestinal bleeding
Recurrent encephalopathy or chronic encephalopathy
Hepatopulmonary syndrome
Portopulmonary hypertension
Intractable pruritus resistant to medical therapies
Miscellaneous liver diseases
Budd-Chiari syndrome
Familial amyloidotic polyneuropathy
Cystic fibrosis
Hereditary haemorrhagic telangiectasia
Polycystic liver disease
Primary oxaluria
Recurrent cholangitis
Uncommon metabolic disease
Malignancy
Cholangiocarcinoma
Hepatocellular carcinoma
Uncommon liver tumours
Other

@MELD score

- Meld score ranges from 6-40 scale which is current calculation for organ transplantation in USA per UNOS (Bilirubin, INR , Creatinine and Na)
- Predict chance of dying within 3/12 in patients with ESLD without LT
- Validated as predictor of survival i no n patients with (cirrhosis, acute liver failure and alcoholic hepatitis)
- MELD 6=10% chance of death in 3/12
- MELD > 20 =25% chance of dying within 3/12
- MELD >40=90% chance of dying within 3/12

Meld score 15 recommended for listing in ESLD
and Delta Meld(change of Meld over time) which is a better predictor of mortality

- Used for organ allocation for liver

transplantation

- Used by UNOs (united network for organ sharing) and Euro transplant to prioritise allocation of liver transplantation instead of CPT
- Development of hyponatraemia in cirrhosis is a marker of Increase waiting list mortality and high risk of neurological dysfunction post liver transplantation

<u>Limitation of MELD score</u>

-Creatinine (ESLD with renal failure increase LT, women at disadvantage due to low mass
-PSC

@Child Pugh Score

- 5 Clinical measurement

2 Minute Medicine®	Child-Pugh Score		2minutemedicine.com
Factor	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Table I. Child-Pugh score.

FRAILITY SCORE

- Muscle wasting
- Functional decline
- Malnutrition

Have significant impact on mortality risk pre and post transplantation
Frailty is a complex syndrome

Fried Frailty Score with 5 components

I. Unintended weight loss
II. Low gait speed-time needed to walk 5 m
III. Exhaustion /weakness
IV. Low physical activity

- Frail(3-5)
- Prefrail(1-2)
- Nonfrail(0)

Weakness/Sarcopenia-assessed by hand grip measures by hand dynamometer

- Frailty powerful predictor of clinical outcomes (decompensation ,hospitalisation or mortality) in patients with ESLD
- All ESLD must undergo assessment of frailty for decision making of critical care or transplantation or prioritisation of rehabilitation (nutrition , exercise physio therapy and psychotherapy)

1. Liver Frailty Index
2. Clinical Frailty Scale

End results of cirrhosis, diabetes , old age is frailty
Subjective clinical assessment of frailty (Eye Ball test)

- Lack objectivity
- Not reproducible
- Lacks consistency

Objective clinical assessment of frailty
Frailty def:
physical state of decrease physiological reserve and increase vulnerability to health stressors
Physical Frailty includes

i. Sarcopaenia

Def. : Generalised loss of skeletal muscle mass
Validated definition of Sarcopaenia in ESLD

Cross sectional imaging assessment of Sarcopaenia

a) CT measured skeletal muscle area at L3 to define Sarcopaenia in ESLD

Skeletal Muscle Index(SMI) especially Psoas Muscle Index (PMI)
Sex defined cut of
SMI <50cm2/m2 in men
SMI <39cm2/m2 in women

Low muscle mass associated with

- Increase in inpatient/hospitalisation
- Increase critical care
- Increase length of stay
- Increase infection complication

b) DeXa scan of appendicular skeletal muscle index ASMI)

- Minimal radiation
- Fat free muscle

c) Ultrasound

- Target iliopsoas muscle and quadriceps
- Challenge in ESLD with ascites and Morbid Obesity

Role in assessing nutritional response

d) Anthropometric

- MidArm Muscle Circumference MAMC)cm)
- Triceps Skin Foldness TSF(mm)
- Mid Arm Circumference (MAMC+3,14 xTriceps Skin Foldness

MAMC predictor of Sarcopaenia and correlate with CT

e) physical function/muscle strength

i. Hand Grip strength

- Dynamometer using no dominant hand
- Assess upper limb strength
- Decreased in transplant await list cohorts

Low HGS associated with

- Increase hospitalisation
- Low physical activity
- Severe liver disease
- Hepatic encephalopathy
- Increase liver related mortality independent of age or aetiology

Every 1kg gained in HGS associated with increase 6% survival rate

ii. Chair stands

- Bed side measure as measure of frailty in ESLD
- Chair stand (rising from sitting position and returning to a seated position)
- Strongest predictor of wait list mortality when use in combination with Hand Grip Strength
- Measures the number of chair stands completed in a set time recorded

Physical function

- Hand grip strength
- Chair stand

Functional capacity

- 6 minute walk test

Physical disability

- Activity of daily living

Sarcopaenic obesity

- Decrease muscle mass/ strength with obesity BMI >30kg-m2
- In NAFLD
- Obesity mask Sarcopaenia/muscle wasting and can go under recognised

ii) Reduced physical function /decrease muscle strength (decrease hand grip strength

- reduced aerobic exercise capacity (decrease ii iii)Minute walking distance , decrease in endurance

iv) Physical disability (decrease in activities of daily living)

Ascites, variceal bleed and hepatic encephalopathy contribute to worsening Frailty

3. Indices for assessment of Physical Frailty

FRIED FRAILTY INDEX

- Takes 10 minutes to assess
- Is 5 point score based on subjective reports
- Exhaustion
- Low physical activity
- Unintentional weight loss)
- Objective report
- Hand grip
- Walk speed)

Score of scale 0-5
0-no frailty
5-most frailty
Every increase in 1 unit in FFI lead to 50% increase in wait list mortality
FFI >3 regarded as Frail reduced activity of daily living

FFI level

- Predict outcome
- Risk stratify those who need intervention like nutrition or tailored exercise

CLINICAL FRAILTY SCALE

- Physical examination of patient or questioning patient/care giver / next of kin
- Quickest frailty score to perform as takes 1 minute to perform with excellent inter observer reliability
- 9 categories ranging from very fit to severe frail (dependent on others for activities of daily living)
- CFS 4 prefail
- CFS 5-9 frailty
- CFS>4 associated with increased hospitalisation and high mortality
- Increase in 1 point associated with increase risk of hospitalisation and death
- Risk stratify patient for more in-depth assessment or pre rehabilitation

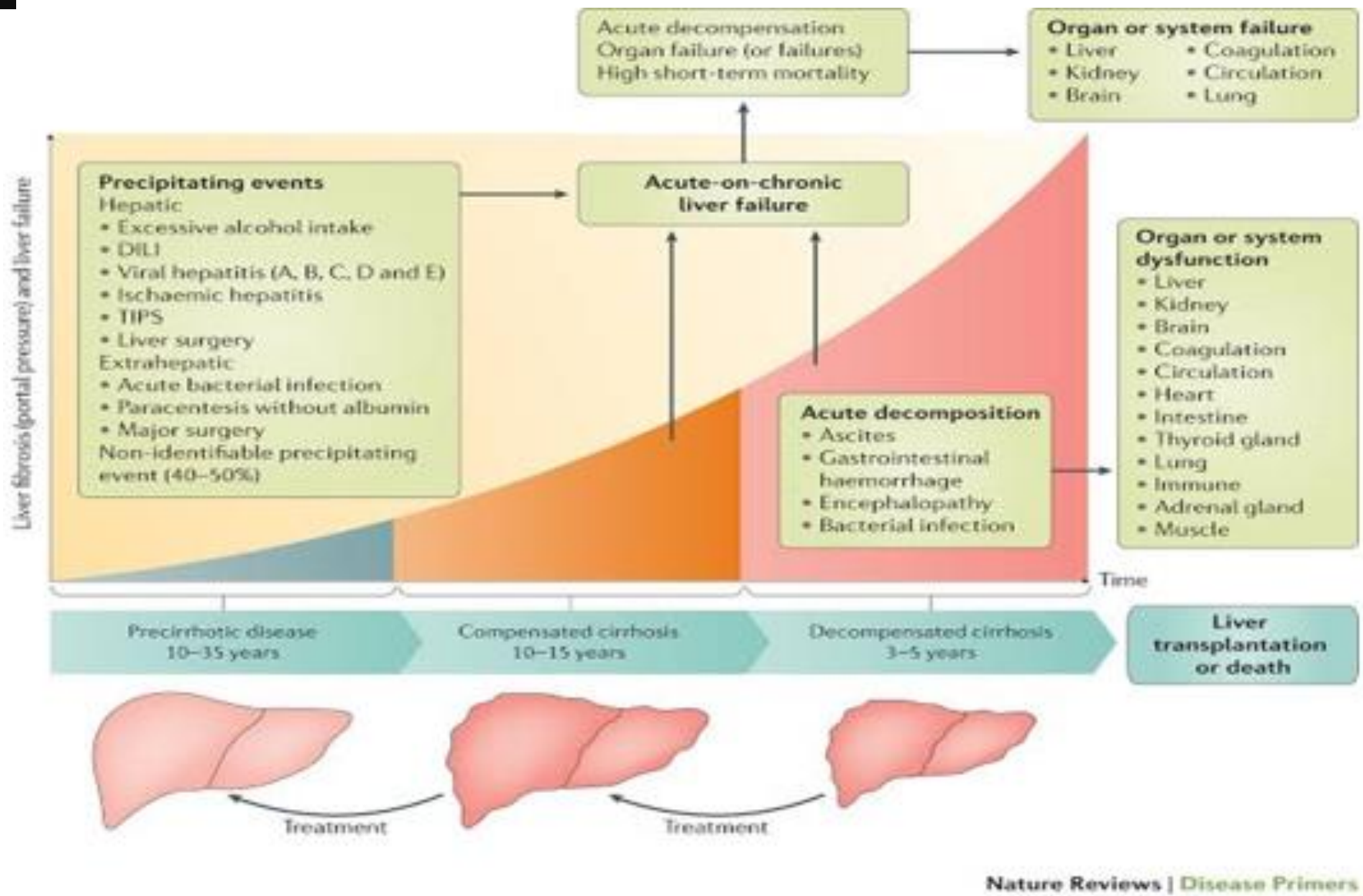
LIVER FRAILTY INDEX

- Metric of 3 performance based measures
- Hand grip strength
- Time to do 5 chair stands in seconds
- Time holding 3 balance position
- Feet side by side
- Feet semi tandem
- Feet in tandem
- Objectively assess physical frailty in ambulatory ESLD

i) ACUTE ON CHRONIC LIVER FAILURE (ACLF)

Def. :Syndrome defined by acute deterioration of liver function (severe liver dysfunction)with associated extra hepatic organ failure requiring intensive care support and high short term mortality

ACLF is a clinical entity with high risk of mortality
ACLF expedite liner transplantation but is associated with short term mobility and mortality post liver transplantation
It leads to multisystem dysfunction and may eliminate patient on waiting list as to sick to undergo liver transplant



Nature Reviews | Disease Primers

CLIF – ACLF organ failure score
CLIF – ACLF score>70 at 48hrs and organ failure predicts mortality in ICU
ACLF prognosis is based on number of organ failure
ACLF 3 more likey to die and are removed from waiting list regardless of MELD score

Organ system	1 point	2 points	3 points
Liver	Bilirubin <103 µmol/L (<6.0 mg/dL)	Bilirubin 103–203 µmol/L (6.0–11.9 mg/dL)	Bilirubin ≥204 µmol/L (≥12.0 mg/dL)
Kidney	Creatinine <134 µmol/L (<1.5 mg/dL)	Creatinine 177–308 µmol/L (2.0–3.4 mg/dL)	Creatinine ≥309 µmol/L (≥3.5 mg/dL) or RRT
	Creatinine 134–168 µmol/L (1.5–1.9 mg/dL)		
Brain (West Haven score)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Vasopressor requirement
Respiratory	PaO_2/FiO_2 >300	PaO_2/FiO_2 201–300	PaO_2/FiO_2 ≤200
	SpO_2/FiO_2 >357	SpO_2/FiO_2 215–357	SpO_2/FiO_2 ≤214

Table 2 Grades of acute-on-chronic liver failure according to the number of organ failure and the type of organ

No. ACLF	
ACLF grade 1	Single- organ failure (coagulation, liver, circulation, lungs) in patients with sCr 1.5-1.9 mg/dL and/or grades 1-2 HE or braine failure with sCr range from 1.5-1.9 mg/dL
ACLF grade 2	Two organ failures
ACLF grade 3	Three or more organ failures

Data from the CANONIC study[12]. ACLF: Acute-on-chronic liver failure; OF: Organ failure.

Goals of treatment

- Rapid recognise and treat inciting events
- Aggressive support of failing organ system
- Treatment by multidisciplinary team with expert in transplant medicine and critical care

Treatment

- Removal or treatment of precipitants
- Appropriate organ failure support

Associated with high mortality, costly ICU admission and requirement of liver transplant

ii) Decompensated cirrhosis and complications

ESLD/Cirrhosis

Primary biliary cholangitis

- 10:1 female to male ratio
- LT not completely cure PBC
- 25% may have recurrent PBC on new liver
- PBC 30% do not respond to UDCA hence need LT
- UDCA has impacted survival significantly
- Early diagnosis and treatment with UDCA has decreased need for LT
- UDCA Progress to cirrhosis 13% rate
- Without UDCA progress to cirrhosis 49%
- UDCA as mono therapy failure rate at 33%

Risk to liver transplantation in PBC

- Late diagnosis
- Late initiation of UDCA
- Inadequate dosing (13-15mg/kg recommended)
- Poor response to UDCA

Indications and timing of liver transplantation for PBC

- Treatment resistant Pruritis
- Recurrent variceal bleed despite preserved liver function
- Decompensated cirrhosis
- Hepatocellular carcinoma
- Mayo risk score > 7.8
- Severe recurrent encephalopathy
- Meld score 12
- Bilirubin >171umol/l

GRAFT SURVIVAL AFTER TRANSPLANT FOR PBC

- Favourable outcome post liver transplant than (autoimmune, Nafld/Nash,Alcoholic)

RECURRENT PBC POST LT

- 25%
- Non specific clinical features
- Rarely Pruritis and jaundice
- Fatigue and metabolic bone disease
- AMA not a marker of recurrence as no correlation between presence of titer of serum AMA and development of recurrent disease

Gold diagnosis

- Histological confirmation of granulomatous cholangitis or florid duct disease
- Inflammatory lymphoplamacytic portal tract disease

Diagnostic criteria for recurrent PBC

- Liver transplant for well described PBC
- AMA positive after liver transplantation
- Liver histology
    - Bile duct destruction
    - Epitheloid granuloma
    - Lymphoid aggregate
    - Mononuclear infiltrates

DIFFERENTIAL DIAGNOSIS BILE DUCT DAMAGE IN GRAFT

- Recurrence of PBC
- Allograft rejection
- Ischaemic injury
- Infections
- Drug damage

Primary Sclerosing Cholangitis

- No effective treatment
- Any age affected but median 35-40 years with 66% men esp without IBD but in female PSC strong association with IBD
- PSC in women older at diagnosis
- PSC associated with IBD in 70-90%
- PSC overlap with AIH in 35% children and 5% in adult
- increase risk of cholangiocarcinoma and colorectal cancer
- Leads chronic cholestatic damage leading to cirrhosis

Account 5% of all liver transplant in PSC in USA

INDICATIONS FOR TRANSPLANT IN PSC

- Decompensated cirrhosis
- Recurrent cholangitis with repeated hospitalisation as associated with higher risk of death
- Intractable itching impairing quality of life
- Long standing severe jaundice
- Cholangiocarcinoma based on tumour location and size

RETRANSPLANT PREPARATION

- Active IBD to be treated before transplant
- Active screening of colon cancer with ulcerative colitis
- Continue with medical treatment of IBD and continue IBD surveillance post LT

PSC RECURRENCE post LT

- 20-30% cases
- 50% recurrence in the 1st year post transplant
- 24,5% recurs at 3years
- 39.3% recurs at 5 years
- Recurrence leads to high graft failure rate

RISK FACTORS FOR PSC RECURRENCE

- High Meld score at time of transplantation
- 1st relative donor recipient relationship
- Post operative CMV infection
- Early biliary anastomoses complication
- High donor age
- History of cholangiocarcinoma
- Untreated associated IBD

POST TRANSPLANT PSC

- Continue IBD treatment and IBD surveillance

WILSON DISEASE

- Genetic metabolic disorder of copper metabolism (ATP7B copper transporter
- Multisystemic disease (liver , eyes , neuropsychiatric)
- Usual age 5-35 years
- Curable when diagnosed early and stop progress to cirrhosis or worsening neuropsychiatric manifestation
- 50% develop liver disease in childhood to their teenage years

Suspected in patient with autoimmune not responding to treatment

Dx with (24hr urinary copper excretion >100ug,low caeruloplasmin, liver Copper content >250ug/g dry weight in adult without cholestasis

HEREDITARY HEMOCHROMATOSIS

- Multisystemic disease (liver , heart, pancreas, joints, gonads and skin)
- 1% will undergo liver transplant
- Increase risk of HCC compared with patients affected by other cause of cirrhosis
- Phlebotomy target ferritin <50ng/ml
- Common cause of death infection 45% and cardiac in 22%

PRETRANSPLANT WORK UP IN HH

- Extensive cardiac work up due risk of cardiomyopathy
- Exclude diabetes

A1ANTITRYPSIN DEFICIENCY

- protein folding disorder leading to toxic insoluble A1antitrypsin protein aggregate in the endoplasmic reticulum of hepatocytes leading to inflammation-fibrosis -cirrhosis
- protein made in liver

deficiency leads to high risk of smoking , dust or pollution lung damage with premature COPD
High risk of cirrhosis and HCC

presentation

- Neonatal cholestasis
- Late onset cirrhosis
- Hepatocellular carcinoma in adults in 5-28%

Diagnosis delayed 5-10years
80-90% unaware of their condition
Misdiagnosed as alcoholic liver disease, NAFLDNash/Cryptogenic cirrhosis

Risk of a1antitrypsin deficiency liver disease progression /acceleration

- Male sex
- Age older than 50 years
- Diabetes mellitus
- Viral hepatitis
- Alcohol
- Nonalcoholic fatty liver disease
- Cystic fibrosis

Triggers for a1 anti trypsin deficiency test

- Unexplained liver enzymes abnormalities
- Cryptogenic cirrhosis
- Hepatocellular carcinoma
- Neonatal cholestasis/hepatitis
- Families history of a1antitrypsin
- Clinical finding of necrotising panniculutia

PRETRANSPLANT WORK UP

- Smoking cessation
- Weight loss
- Stop alcohol
- Avoid NSAIDs
- HCC Screening
- Pulmonary work up

LIVER TRANSPLANT A1antitrypsin

- Curative option for a1antitrypsin deficiency liver disease
- Represent 1%of all liver transplantation with excellent 5 year graft and patient survival rates

FAMILIAL AMYLOIDOTIC POLYNEUROPATHY

- Common in Portugal
- Rare progressive degenerative disorder and life threatening disease inherited as autosomal dominant pattern
- Mutation of transthyretin (TTR)
- Progressive peripheral and autonomic polyneuropathy
- Liver transplantation early only proven disease modifying treatment to disease and the liver can be donated on Domino surgical procedure to another person

AUTOIMMUNE HEPATITIS

- 10-20% of autoimmune hepatitis will eventually need liver transplant
- Account for 5% and 2-3% liver transplant in USA and Europe
- Frequency of acute and chronic rejection after liver transplant for autoimmune hepatitis more frequent compared to other liver disease

Indications to LT

- Acute liver failure
- Decompensated cirrhosis MELD score >15
- Hepatocellular carcinoma
- Inadequate response
- Intolerance to immunosuppressive therapy

Cirrhosis develop

- Incomplete response to treatment
- Treatment failure
- Multiple relapses

Outcome with liver transplantation favourable with 5 year survival 80%

Risk

a) Recurrence Autoimmune Hepatitis
(development of the same disease in the allograft following liver transplantation)

- Autoimmune hepatitis recurs in 36-68% of recipients at 5 years after LT with high risk of allograft loss and re transplantation
- Not affected by allograft type
- Work up same like original disease and equally challenging

Challenging

- Absence for specific marker for diagnosis
- Immunosuppression therapy may mask features of the original disease
- Disease progression may differ and lead to atypical presentation

<u>Risk factors for recurrence AIH</u>

Recipient factors

- Higher titers of autoantibodies at the time of LT
- Coexisting autoimmune disease
- Severe necroinflmmatory activity in the explanted liver at the time of transplantation

Therapy factors

- Early corticosteroid withdrawal (no adherence or physician recommendation)

Recurrence AIH need prompt treatment as 50% of cases are resistant therapy leading to graft failure and loss
Retransplant required in 33-60% cases if severe

b) Denovo Autoimmune Hepatitis
(Development of autoimmune hepatitis like in a patient who had undergone liver transplantation for the cause other than autoimmune hepatitis)

HEPATOCELLULAR CARCINOMA

- ost common primary malignancy of the liver
- 3rd leading cause of cancer related death world wide

Risk

- Cirrhosis of liver
- Chronic hepatitis (50% hep B and 25% hep C)
- Toxin(alcohol, aflatoxin B, hemochromatosis)
- Metabolic (NASH 20% , diabetes type 2)
- Alpha 1 antirypsin
- Wilson disease
- Biliary disease
- Liver transplantation for early or unresectable HCC in the setting of chronic liver disease

Milan criteria only in cirrhotic liver

- Solitary HCC nodule <5cm
- 3 nodules with diameter <3cm
- No angioinvasion
- No extrahepatic involvement

Post liver transplant based on Milan criteria have excellent results with 5 year survival >70%
Liver transplant with intention to cure the disease

CHOLANGIOCARCINOMA

- 2nd after HCC
- Account 5-20% of liver malignancies
- High risk of recurrence
- Neo adjuvant chemo radiation +liver transplantation
- Liver transplantation for perihilar cholangiocarcinoma

OTHER HEPATIC NEOPLASM

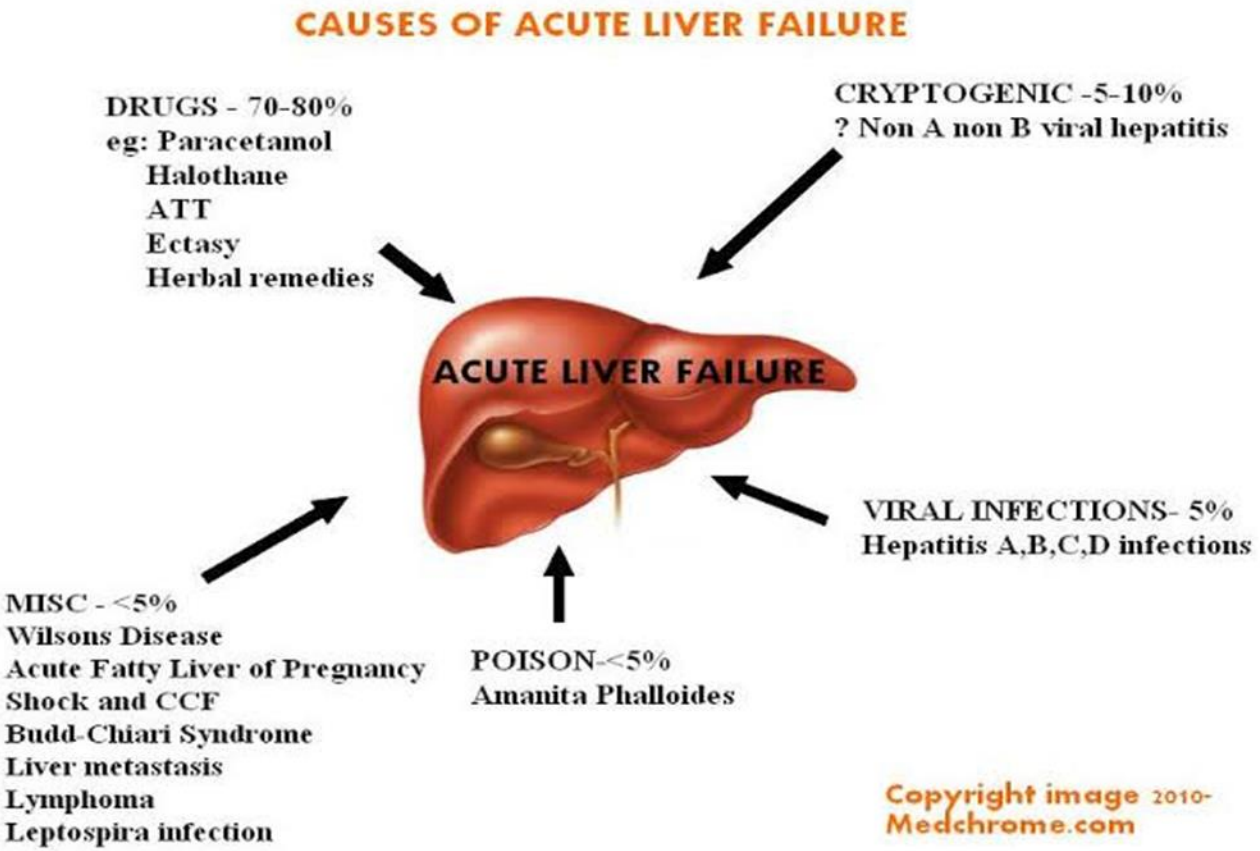
- Neuro- endocrine tumours indications for LT
- Diffuse metastasis of the liver
- Symptoms of hormone production
- Symptoms related to massive hepatomegaly
- Patient has no extrahepatic tumour

Colorectal cancer -unresectable metastasis controversial

ACUTE LIVER FAILURE

Definition of Acute Liver Failure
International normalized ratio (INR) ≥ 1.5
Neurologic dysfunction with any degree of hepatic encephalopathy
No prior evidence of liver disease
Disease course of ≤ 26 weeks

Table 2. Definition of Acute Liver Failure (ALF)



Account 8 -11% of indications for liver transplant
Prior liver transplant mortality 80-85%
King College Hospital criteria used for listing patient with acute liver failure for liver transplantation
MELD useful for assessing prognosis in acute liver failure in non paracetamol
MELD > 30 excellent predictor of mortality in patients with non paracetamol cause(viral , drug induced , Cryptogenic)

High mortality rate of 50-90% justifies early transfer to specialised center with liver transplant

Predictive parameters is extent of cerebral dysfunction is a determine factor of survival rate
Hepatic encephalopathy grade 1(94% survival rate) grade 4 (11% survival rate)

Acute liver injury
Criteria

- Normal level of consciousness
- Coagulopathy of liver origin

Multisystem disorder triggered by acute liver failure with marked activation of systemic inflammatory response which can extend into post transplant period

- Urgent indications for LT , account 8% for LT

<u>Determinants of prognosis of acute liver failure</u>

- Underlying aetiology
- Age of patient
- Degree of coagulopathy,
- Neurological status /encephalopathy
- Extend of damage to other organs
- King College criteria

Indicators of poor prognosis

- Underlying cause/ aetiology
- Encephalopathy
- Symptoms duration (hyper acute , acute or subacute)
- Age (children rare encephalopathy and usually an ominous sign
- Serum bilirubin
- INR/PI/PT of 90s and INR >4 mortality exceeds 90%

Hyper acute

- Onset of hepatic encephalopathy within 7 days of symptoms

(Short term transplant free survival is 30%)

Acute

- Onset of hepatic encephalopathy is between 8-28 days of symptoms

(Short term transplant free survival is 33%)

Subacute

- Onset of encephalopathy after 28days of symptoms

(Short term transplant free survival is worse at 14%)

Sequela of ALF

- Cerebral oedema
- Coagulopathy
- Renal failure
- Metabolic disturbance
- Infection

ENCEPHALOPATHY AND CEREBRAL OEDEMA IN ACLF

- Type A type of encephalopathy
- Severe liver disease causing nervous system disorder
- Graded by West Haven grading system

Clinical grading of hepatic encephalopathy	
Clinical grade	**Clinical signs**
Grade 1	Poor concentration, slurred speech, disordered sleep rhythm
Grade 2	Drowsy, occasional aggressive behavior, lethargic
Grade 3	Marked confusion, gross disorientation
Grade 4	Unresponsive to voice, unconscious

Grade 1&2 good prognosis
Grade 3&4 bad prognosis needing ICU
admission, intubation and preservation of cerebral perfusion pressure to prevent Ischaemia

- Most lethal complication leading to uncial herniation and death
- Diagnosis of exclusion

Do CT brain , MRI and EEG

EEG findings
- Progressive suppressed alpha rhythms

Treatment

- Lactulose and bacterial decontamination of GI with Neomycin not effective in ACLF consider Rifaximin
- Intubation
- Intracerebral pressure measure directly
- Maintain cerebral perfusion pressure at 40mmmHg
- Mannitol , hypertonic saline
- Sedation
- Hypothermia

COAGULOPATHY IN ACLF

- Measured by Prothrombin Time (PT)
- Complicates spontaneous haemorrhage (GIT)

Treatment

- FFPs if bleeding
- Plasmapheresis for acute liver failure plus life threatening bleeding

RENAL FAILURE IN ACLF

- Multifactorial
- Drugs (paracetamol and non paracetamol
- Disease (Wilson disease, viral hepatitis
- Volume depression
- Hepatorenal (intense vasoconstriction of renal cortical vasculature with resultant oliguria and Na retention
- Sepsis

May need haemodialysis due to renal failure
Continuous haemodialysis is preferred to intermittent to avoid large variations in volume status

ACLF SEPSIS

- ACLF is functional immunosuppression
- Bacteria and fungi are detrimental

Risk of infection

- CVP lines
- Mechanical ventilation

Infection associated with worsening encephalopathy
60% of patients with acute liver failure will become infected and develop SIRS
No utility of prophylactic antibiotics in ALF not established

METABOLIC DISORDER IN ACLF

- Hypoglycaemia

High insulin
Impaired gluconeogenesis

- Metabolic acidosis

Global hypo perfusion
Lactate

- Hyponatraemia
- Hypophosphataemia
- Alkalosis

CARDIOVASCULAR IN ACLF

- ACLF like systemic sepsis
- Vasodilation and increase cardiac output due to circulating endotoxins and TNF

Decrease in volume compounds effect of ALF

Hypotension ensues poor prognosis as lead to low cerebral perfusion pressure thus deepening encephalopathy

- Hypotension
- Arrhythmia (electrolytes)

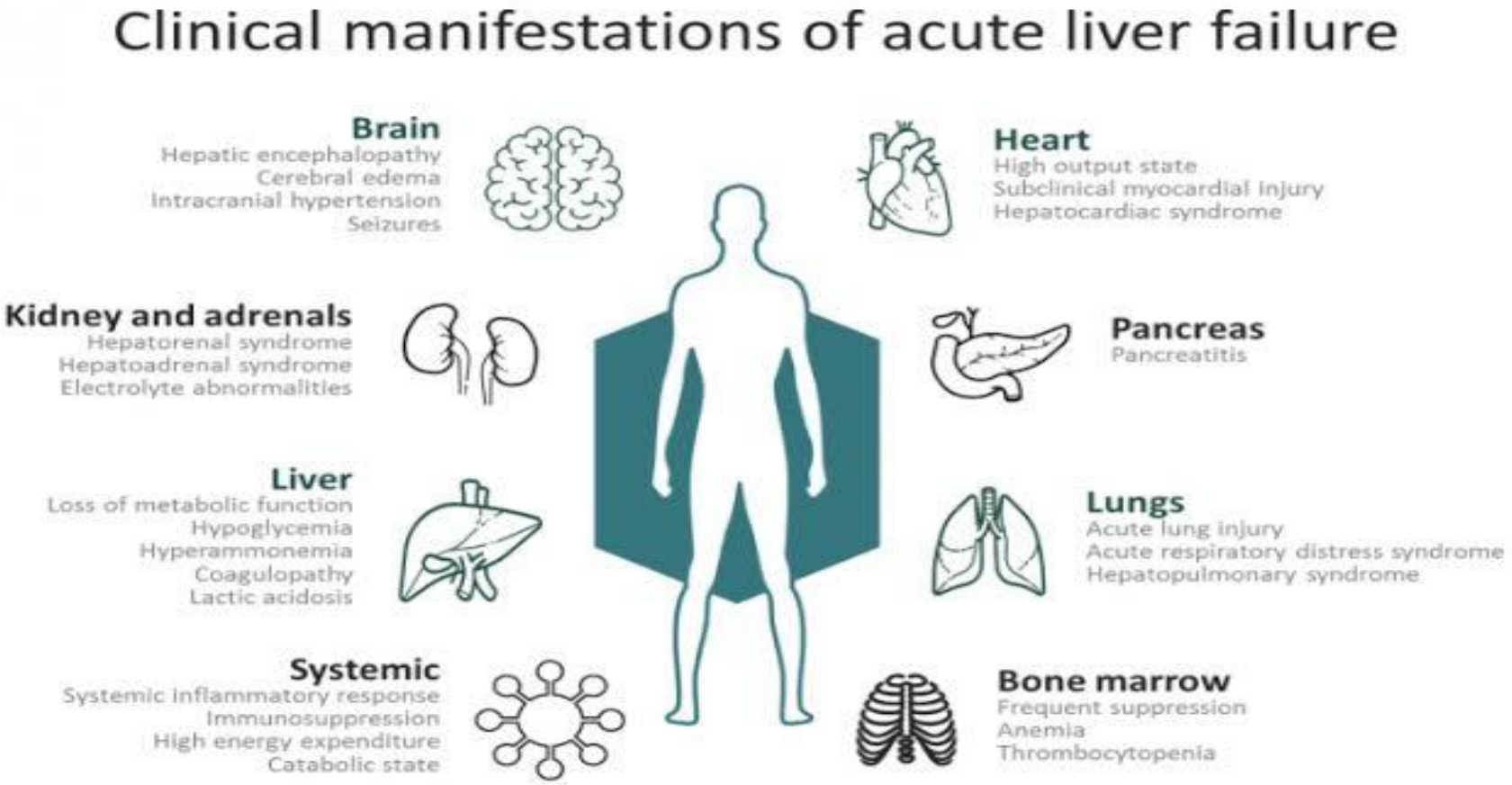


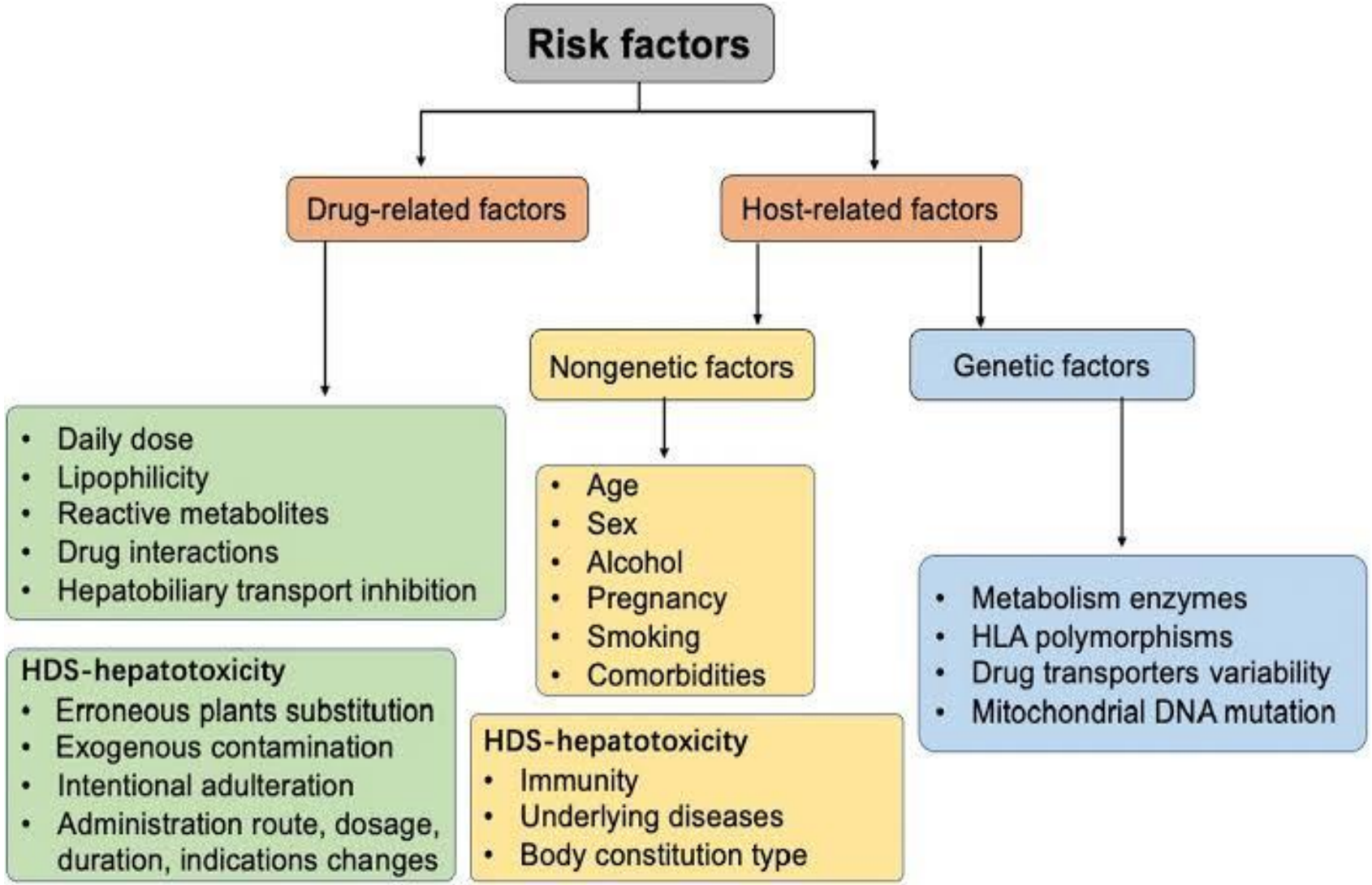
Figure 1. Clinical manifestations of acute liver failure

Drug induced liver failure

- Account for 50% of ALF/fulminant DILI
- Paracetamol toxicity in majority
- Diagnosis of exclusion (viral ,autoimmune, alcoholic hepatitis, fulminant Wilson disease, acute Budd chiari syndrome, Ischaemic hepatitis and Cholestatic hepatitis)
- Acetaminophen over dose account for 50% who underwent liver transplant for drug induced ALF
- Non paracetamol drug induced account for 3% of liver transplant

Risk factors

- Old age >50
- Female
- Obesity
- Diabetes
- Pre-existing alcohol use
- Pre-existing hepatotoxins
- Concomitant hepatitis
- Nutritional status
- Smoking


Risk factors
Drug-related factors
Host-related factors
Nongenetic factors
Genetic factors
• Daily dose
• Lipophilicity
• Reactive metabolites
• Drug interactions
• Hepatobiliary transport inhibition
HDS-hepatotoxicity
• Erroneous plants substitution
• Exogenous contamination
• Intentional adulteration
• Administration route, dosage, duration, indications changes
• Age
• Sex
• Alcohol
• Pregnancy
• Smoking
• Comorbidities
HDS-hepatotoxicity
• Immunity
• Underlying diseases
• Body constitution type
• Metabolism enzymes
• HLA polymorphisms
• Drug transporters variability
• Mitochondrial DNA mutation

Severe DILI Hys law

- AST /ALT >3ULN
- Bilirubin 2ULN without cholestasis
- Poor prognosis with 10-50% mortality in pretransplant
- Paracetamol non paracetamol
- King College criteria

Acetaminophen-induced ALF	Nonacetaminophen-induced ALF
Arterial pH <7.30 after fluid resuscitation	Prothrombin time >100 sec (INR >6.5)
Or all of the following: • Prothrombin time >100 sec (INR >6.5) • Serum creatinine >3.4 mg/dL • Grade 3 or 4 hepatic encephalopathy	*Or* any 3 of the following: • Non-A, non-B viral hepatitis, drug-induced or indeterminate etiology of ALF • Time from jaundice→ encephalopathy >7 days • Age <10 years or >40 years • Prothrombin time >50 sec (INR >3.5) • Serum bilirubin >17.4 mg/dL

Fulminant viral hepatitis

- 60% hep B coinfected with hep D
- 40% hep E
- Rare Hep A
- Herpes , CMV

Hep A undergo spontaneous recovery unless underlying liver disease
Hep B fulminant-Nucleotide analogues

Acute severe Autoimmune hepatitis with ALF

- Idiopathic or drug induced
- Uncommon presentation
- 50-60% of AS -AIH progress to AS-AIH with ALF
- Acute decompensation with superimposed acute injury in pre-existing chronic liver disease with extra hepatic organ failure

AIH ALF difficult to distinguish from Acute on Chronic Liver Failure

Precipitants

- Heavy alcohol intake
- Drugs
- Viral hepatitis
- Infection/sepsis
- Haemorrhage
- Ischaemic hepatitis

Treatment

- Treat Precipitants
- Organ support
- Liver biopsy

Predictors of response to corticosteroids

- Low grade hepatic encephalopathy
- Absence of massive hepatic necrosis on histology
- Meld score <27

Predictors of failure to respond to steroid

- MELD score >27
- INR>2.46
- Severe fulminant form of Autoimmune hepatitis
- HLA DR B1*03

Assess response once steroid commenced

1. Transaminases activity
    - AST /ALT not useful markers of response once steroid started due low production due to disease severity and poor hepatocyte regeneration

2. Bilirubin and INR

- Better markers of response
- Failure to improve pre-treatment hyper bilirubin after 2/52 of corticosteroids associated with early mortality
- INR >2 with hepatic encephalopathy and deteriorating bilirubin and INR after 4 days of corticosteroids treatment associated with poor outcome
- Failure to respond at day 7 likely no response
- 20% increase in Prothrombin Time at day 3 associated with poor prognostic marker

3. Change in prognostic indices (MELD Na)

- Failure to improve MELD Na on day 7 of corticosteroids indicates high risk progression to acute liver failure

Need for reliable prognostic predictors to facilitate patient selection for liver transplantation
Bilirubin/ INR/Meld Na after day 7 of steroid no response prepare and assess for liver transplantation

<u>Corticosteroids complication</u>

- ALF is functional immune suppressive state and corticosteroids propagate bacterial septicaemia / fungaemia hence complicate liver transplantation process
- Cumulative incidence of infection increased exponentially from induction phase

Liver transplantation in AS AIH

- AS-AIH spontaneous recovery low 7-15%
- LT effective rescue therapy
- Not delay LT by protracted courses of corticosteroids
- During trial of steroid , simultaneous transplant assessment must run parallel
- Assess corticosteroids response early as disease course crucial in deciding the right time to pursue LT before septic complications and irreversible brain injury
- Proceed to urgent listing-multidisciplinary team

Outcome of LT AS-AIH / AS-AIH ACLF

- 1 year survival 80-94%
- Increase rejection as opposed to non AIH
- Recurrence common post LT at 7-12% of transplanted patient at 1year and 36-68% at 5 years

Determinants of Recurrence

- Increased liver enzymes
- Increased immunoglobulin's
- Pretransplant serology
- Histology of explanted liver (lymphoplasmacytic infiltration with moderate to severe inflammatory activity in explants is associated with greater probability of recurrent AIH

Summary

AS AIH rare disorder
True incidence not defined
Account to 5% and 2-3% of liver transplantation in USA and Europe respectively
High risk of acute or chronic rejection after liver transplant for AIH compared to others
5 year survival of patient and graft is 80-90% and 72-74%

Diagnostic challenge

- Nonspecific symptoms
- Identification of serology as autoantibody positivity be interpreted with caution
- Always compounding viral and drug triggers

Account for proportion of patients with indeterminate or sero negative ALF
Typical scoring system for AIH is obsolete in AS-AIH
Early liver biopsy is informative ideally before severe coagulopathy or high grade hepatic encephalopathy
CT scan asses liver volume

Indications for transplantation in AIH

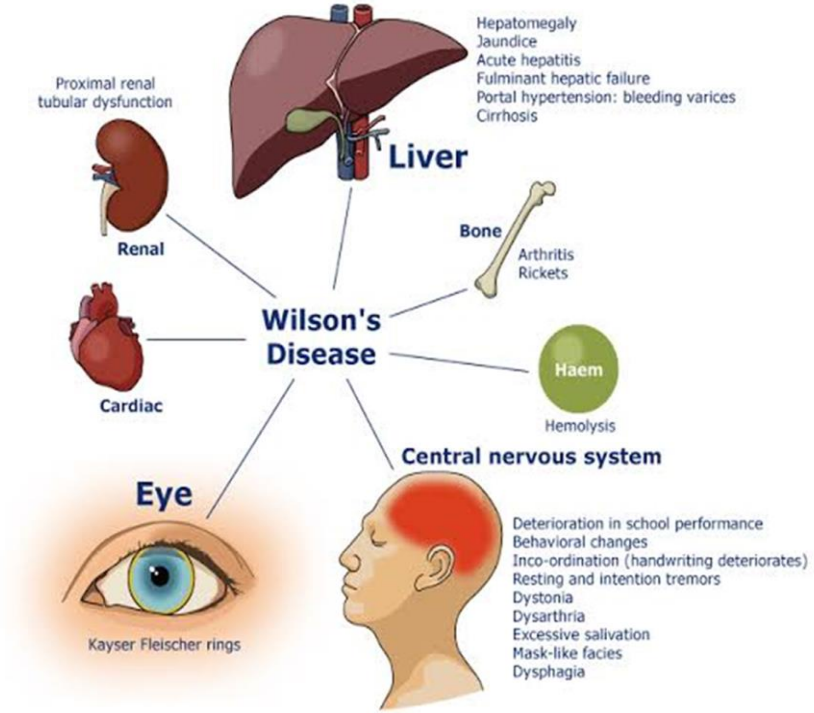
- Inadequate response to treatment
- Intolerance to immunosuppression
- Acute severe Autoimmune hepatitis with Acute liver failure
- Acute on chronic liver failure
- Complication of cirrhosis
- Hepatocellular carcinoma

AIH post liver transplant

a) Recurrence of autoimmune hepatitis
    - 1st year (8-12%)
    - 5 years (36-68%)
    - Not affected by allograft type (cadaveric or LD)
    - Work up same like original but challenging like (absence of specific marker for diagnosis, immunosuppressant mask features of original disease,)

FULMINANT WILSON DISEASE IN ACLF

- Most common inherited liver disease , autosomal recessive genetic metabolic disease of copper metabolism
- 1 in 37 000
- Curable disease
- Early diagnosis to stop progression to Cirrhosis/Neurology / Psychiatric and Ocular
- Hepatic manifestations extremely variable
- Fulminant liver failure occurs only in 5% of cases
- Diagnosis is important due to high mortality without liver transplant
- It has implications for family member
- Diagnosis of Wilson in ALF challenge



Acute liver failure Organ Transplant Network make special provisions for acute liver failure due to Wilson disease when considering for urgency of transplantation

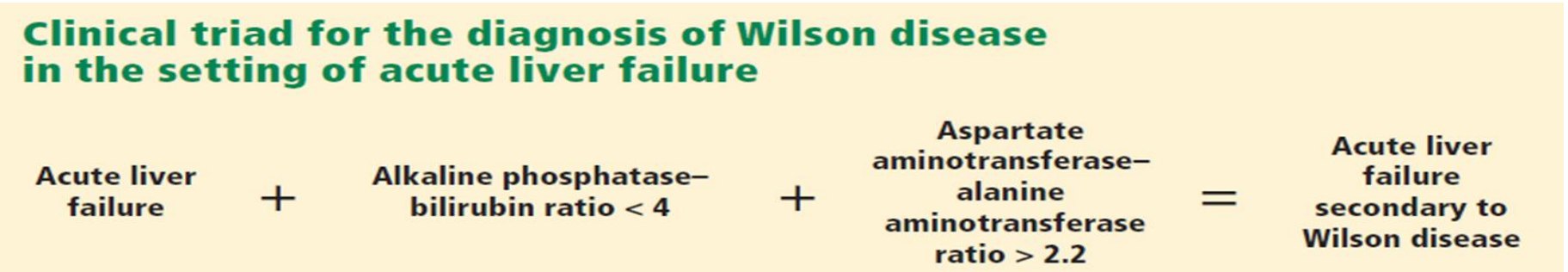
ALF setting of Wilson difficult diagnose

- Copper parameters less sensitive and specific
- KF rings rarely identified in 50%
- Slit lamp exam in critical ill patient difficulty
- Renal dysfunction in 40% cases hence urinary copper utility limitation
- Liver biopsy for hepatic copper level is not practical due to high risk of bleeding
- Time for genetic assessment is limited

Suggestive of fulminant Wilson in ACLF

- Mild increase in serum transaminases compared to degree of hepatic insufficiency
- Higher serum bilirubin concentration
- Coombs negative hemolytic anaemia(strong association with ACLF of fulminant Wilson disease

Rapid diagnostics WD in ALF



- 2 index scores are used
    1. Ratio of ALP/total bilirubin < 2 AASLD or <4 EASLD
- ALP is decreased in acute presentation of Wilson disease but there is increased Bilirubin concentration
- Sensitivity of 94,9% and specificity of 94%

    2. Ratio of AST/ALT >4 or >2.2
- Concept of mitochondrial injury in fulminant Wilson disease
- Sensitivity of 94% and specificity of 86%

ALP/total bilirubin ratio <4 and AST/ALT ratio >2.2 together sensitivity and specificity increases up to 100%

- High serum and urinary copper concentration

Above helps to distinguish Wilson from other ALF aetiology
- Low caeruloplasmin level
- KF ring by slit lamp

NAZER PROGNOSTIC INDEX

Lab measurement	normal value	Score 0	Score 1	Score 2	Score 3	Score 4
Serum bilirubin	0.2-1.2	<5.8	5.8-8.8	8.9-11.7	11.8-17.5	>17.5
SGOT	10-35	<100	100-150	151-200	201-300	>300
PT prolongation diff.	12-14s	<4s	4-8s	9-12	13-20	>20

Nazer score or Wilson index helps risk stratify patient needing liver transplantation or benefit from medical therapy
Score / index sensitive and specific at predicting mortality without liver transplantation
Revised Wilson Index added WCC and serum Albumin

Minimum 3
Moderate 6
Severe 9
Scores of 7 or higher predicts a fatal outcome

Score Max 12
<7 -medical treatment
7-9=clinical judgement
>9=immediate liver transplantation

Acetaminophen	Nonacetaminophen
pH <7.3	PT >100 s (INR >6.5)
Or all three of: Grade 3–4 encephalopathy PT >100 s (INR >6.5) Cr >3.4 mg/dL	Or any three of: Age <10 or >40 y Etiology (non-A, non-B hepatitis, halothane, drug reaction, Wilson disease) Period of transition from jaundice to encephalopathy <7 d PT >50 s (INR >3.5) Total bilirubin >17.5 mg/dL

Indications for liver transplantation

- Unresponsive to medical therapy
- Cirrhosis
- Fulminant hepatic failure
- King College non paracetamol
- Meld score
- Nazer index / Revised Wilson Index

NB neurological complications for liver transplantation is highly controversial and not recommended

Liver transplant 5 year survival is >85%

Exclude

- Viral hepatitis (hep A IgM and IgG/ Hep B sAg eAg core IgG/ Hep C IgM and IgG PCR/ CMV , Herpes /EBV, Varicella
- Autoimmune hepatitis (fail to respond rapidly and appropriate corticosteroids , ANA and AntiSmooth muscle antibodies
- Drug induced hepatitis (paracetamol drug level)
- Celiac hepatitis
- IgG4 hepatitis
- Ischaemic hepatitis

Pre liver transplant work up in Wilson Disease

- Neuro psychiatric assessment
- Ophthalmologist (!slit lamp)
- Cardiac evaluation (ECG abnormalities/cardiomyopathy, orthostatic hypotension)
- Renal for renal tubular disease and urolithiasis
- Hepatic blood flow with Doppler ultrasound
- Liver biopsy
- CT scan

Liver support system in fulminant hepatic Wilson

- Plasmapheresis with FFP replacement has efficacy to decrease seru copper levels
- Molecular adsorbent Recirculating System (MARS)
- Albumin dialysis
- Chelating drugs (D Penicillamine +Trientine) that promote renal copper excretion usually in stable Wilson disease but in fulminant disease and rapidly progressive renal failure benefit is unclear

When to consider liver support system as bridge to transplant

- Encephalopathy grade 3&4
- Serum bilirubin >250
- Increase transaminases by >50% in consecutive days
- Serum ammonia level over standard range
- Serum creatinine or urea over standard range

ACUTE ALCOHOLIC HEPATITIS

TABLE 1

Consensus Definition of Alcoholic Hepatitis

Diagnostic criteria

- Jaundice onset within previous 8 weeks
- Long-term consumption of alcohol: > 40 g (roughly 3 standard drinks) daily for women or > 60 g (roughly 4 standard drinks) daily for men for ≥ 6 months, with < 60 days of abstinence before onset of jaundice
- AST > 50 U per L (0.83 µkat per L), AST/ALT ratio > 1.5, and both AST and ALT < 400 U per L (6.68 µkat per L)
- Total bilirubin > 3 mg per dL (51.31 µmol per L)
- Absence of confounding factors

Confounding factors

- Possible ischemic hepatitis (suggested by severe upper gastrointestinal tract bleed, hypotension, cocaine use within seven days of symptom onset)
- Possible metabolic liver disease (Wilson disease, $alpha_1$-antitrypsin deficiency)
- Possible drug-induced liver disease (use of offending drug within 30 days of jaundice onset)
- Uncertain alcohol use assessment (patient denies excessive alcohol use)
- Atypical laboratory findings (AST < 50 U per L or > 400 U per L, AST/ALT ratio < 1.5, antinuclear antibodies > 1:160, or anti–smooth muscle antibodies > 1:80)

If diagnostic confirmation would change management in the presence of confounding factors, perform liver biopsy

ALT = alanine transaminase; AST = aspartate transaminase.

Information from references 1, 7, and 10.

Fever
Tachycardia
Tender hepatomegaly
Leukocytes
Exclude Hepatocellular carcinoma, hepatic liver abscess and biliary obstruction
Prognostic score
Maddrey score >32
Meld score > 18 AASLD
Glasgow Alcoholic Hepatitis Score (age ,bilirubin,PT , urea and WCC)
Lille score D4 < 0,45

Biopsy if

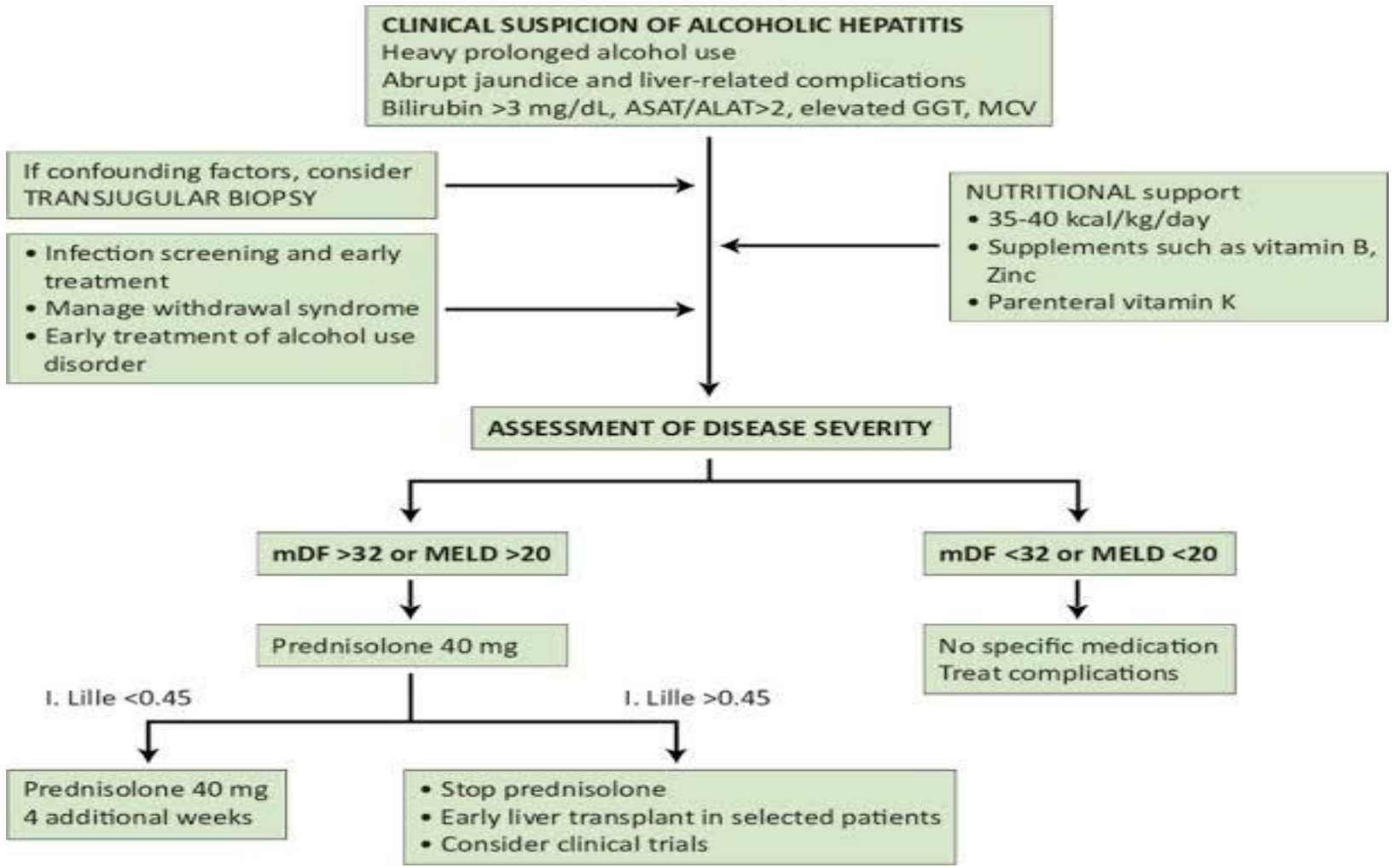
- Clinical diagnostic doubt
- Concern for dual pathology

<u>Rational for liver transplantation in Alcoholic Hepatitis</u>

- High short term mortality
- Lack of available effective medical treatment
- Liver transplantation only salvage option as per EASLD

Liver transplantation for severe Alcoholic Hepatitis Controversy

- Organ shortage
- Risk of relapse 15-40%
- Self inflicted disease


CLINICAL SUSPICION OF ALCOHOLIC HEPATITIS
Heavy prolonged alcohol use
Abrupt jaundice and liver-related complications
Bilirubin >3 mg/dL, ASAT/ALAT>2, elevated GGT, MCV
If confounding factors, consider TRANSJUGULAR BIOPSY
• Infection screening and early treatment
• Manage withdrawal syndrome
• Early treatment of alcohol use disorder
NUTRITIONAL support
• 35-40 kcal/kg/day
• Supplements such as vitamin B, Zinc
• Parenteral vitamin K
ASSESSMENT OF DISEASE SEVERITY
mDF >32 or MELD >20
mDF <32 or MELD <20
Prednisolone 40 mg
No specific medication
Treat complications
I. Lille <0.45
I. Lille >0.45
Prednisolone 40 mg
4 additional weeks
• Stop prednisolone
• Early liver transplant in selected patients
• Consider clinical trials

SELECTION CRITERIA FOR ALCOHOL HEPATITIS LT

- Likely to die without liver transplant

Inclusion criteria

- Maddrey Discriminant Function >32
- Non-responder to (according to Lille ≥0.45) or ineligible for medical therapies (mainly corticosteroids)
- First liver-decompensating event
- Favourable psychosocial profile
- Good social support
- Agreement of transplant selection committee

Exclusion criteria

- Uncontrolled infection
- Comorbid systemic illness likely to prevent recovery
- Poor prognostic profile: failure to accept addiction as a problem; history of previous failed alcohol use disorder treatments
- Lack of social support: no home, supporting family or friends, lack of transport
- Prior liver-decompensating events
- Severe, uncontrolled psychiatric disorder

High risk patient of relapse post LT

- >10 drinks /day at initial hospitalisation (4 points)
- Multiple prior rehabilitation attempts (4 points)
- Prior alcohol related legal issues (2points)
- Prior illicit substance abuse(1points)

Score <5 have 95% negative predictive value for sustained alcohol use post LT
SIPAT(Standford Integrated Psychosocial Assessment for Transplantation

- Another scoring system
- Assess patient readiness level

Variables identify patients at high risk

1. Knowledge and understanding of medical illness process(4 points)
2. Knowledge and understanding of process of transplantation (4points)
3. Willingness and desire for treatment/transplant (4 points)
4. History of treatment adherence(8 points)
5. Life style factor (4 points)

Post Liver transplantation in alcoholic hepatitis

-6/12 survival after liver transplantation is 77%vs 23 % if no transplantation
-If patient sustain abstinence after LT the 1 year survival rate is 94% and 3year survival rate at 84%
-Post transplant risk of invasive fungal infection within 2 weeks of transplant

HEPATOCELLULAR CARCINOMA

a)HCC (Hepatocellular carcinoma)
-5th most common cancer in the world
-70-90% develop in background of cirrhosis / chronic inflammation
-MELD exception needing extra points to access liver transplantation
-use size of tumour, number of nodules , location , alpha feto protein, response to down staging therapy

Milan criteria for liver transplantation

- One lesion smaller than 5 cm.
- Up to 3 lesions smaller than 3 cm.
- No extrahepatic manifestations
- No vascular invasion

EVALUATION OF LIVER TRANSPLANTATION

1.Exclude major comorbid condition precluding successful liver transplantation
2.Exclude alcohol or substance abuse disorder
that has impact on adherence to a complicated and life long medical regimen
3.Exclude psychosocial issues
4.Exclude treatable medical comorbidities or psychological problems pretransplant to improve post transplant outcome
5.Confirm irreversible nature of patient disease
and lack of effective medical therapy ,duration, complications and severity and impact of liver disease on patient functional level
6.Medical history, exam and risk appropriate cardiopulmonary evaluation
7.Laboratory evaluation
-Hepatic function
-Renal function
-Viral studies(hep ABC,CMV , EBV, HIV
8.Abdominal Imaging (Doppler Ultrasound CT MRI) for patency of vasculature and exclude HCC(size, number, vascular invasion and metastasis)
9.Psychological evaluation
10.Prophylaxis (vaccination hep A and B , variceal hemorrhage
11.Discuss recurrence of disease after transplantation
12.HCV antiviral therapy and drug interaction pre and post transplant

Surgical evaluation
-Obesity
-Prior abdominal surgery
-Educate family about (donor and graft types,complexity of surgery, potential complications, rejection rates , immunosuppression and long term side effect

A. Nutritional assessment and management pre LT
a)Malnutrition
-Cirrhosis leads to malnutrition and cachexia in 70%
-Associated with lower survival post liver transplant
-BMI <18.5 high risk of poor outcome
-Assess sarcopenia by CT evaluation of transversal psoas muscle thickness
-Key predictor of succesful liver transplant
-Assess (height , weight , triceps skin fold thickness (measure adiposity, mid arm circumference (measure lean body mass) at least every 3/12 while awaiting transplant
-Weight gain limitation (hepatosplenomegaly, ascites and oedema)
-EASL Frailty Sarcopaenia CT L3 Skeletal Muscle Index SMI / Psoas Muscle Index PMI
Identify HCC, biliary anatomy, hepatic vasculature

b)Obesity
-BMI>40 associated with worse outcome
-Associated with metabolic syndrome and diabetes
high risk risk of post transplant diabetes and cardiovascular events
Pretransplant diabetes and dyslipidaemia need to be managed

B. Hepatitis B related liver disease

Indication for treatment with Nucleot(s)ide analogue

-Cirrhosis irrespective of HBV viral load
-Acute fulminant liver failure
-Hepatocellular carcinoma

Pretransplant

-Nucleiotide analogue with high genetic barrier (Tenofovir or Entecavir) as 1st choice
-Entecavir in Meld >20 high risk of lactic acidosis

Benefit of Hep B treatment pre transplant

-May improve liver function test and decrease risk of decompensation
-Decrease HBV recurrence post transplant
-Decrease risk of Hepatic cancer

33% might improve liver function and be Delisted and avoid liver transplantation
Despite effective antiviral treatment 25% of cases deterioration of liver function and death in 6/12

-oral antiHep B for Hep B viral suppression Tenofovir based (high genetic barrier to resistance)

C. Hepatitis C related

-50%of liver cancer in USA related to HCV
-Cirrhosis due to HCV indication for liver transplantation in Europe USA and Japan
-Untreated HCV may complicate liver with (severe liver disease, cirrhosis and liver cancer)
Recurrence of Hep C post transplant and factors that accelerate liver disease post transplant
-High viral load at time of transplantation
or soon after surgery
-Infection with genotype 1b or 4
-Ischemia time(if re warm > 90minute 65% severe hep C , >30minutes 19% severe hep C
-Female gender

25% of transplant recipients develop cirrhosis in grafted liver within 5 -10years compared to 10-40 years in no transplant

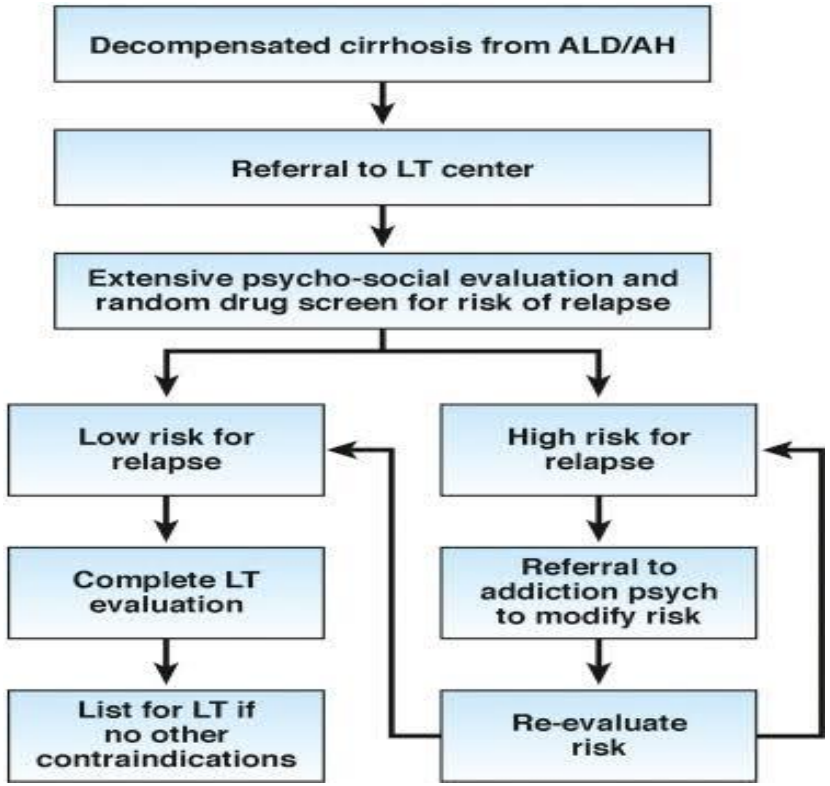
Benefit of treatment
-Waiting list has decreased for Hep C related complications due DAA
-Post HCV cirrhosis transplant has decreased by 53% due to DAA
-Treatment associated with improvement in liver function and some delisted
-Helps prevent infection of new liver

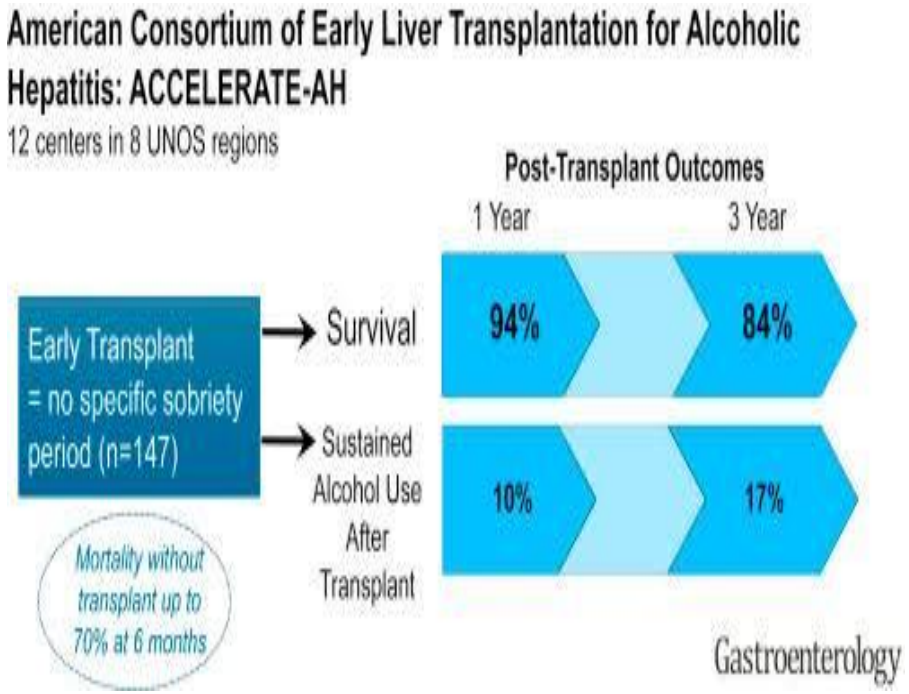
Factors accelerate liver disease after transplant
-High viral load at time of transplant or soon after surgery
-Infection with genotype 1 esp 1b
-Age of donor liver
-Female gender
-Ischaemic time(amount of time liver kept on ice without O2 support after its long removal from the donor
If >30 minutes-19% risk of severe hepatitis C
If >90minutes-65% risk of severe hepatitis C

D. Alcohol related liver disease (cirrhosis and acute alcoholic hepatitis)
-Common indications for LT in western world
-Abstinence for 6/12 non consensus
-Risk of relapse is 15-40%

Benefit of 6/12 abstinence

- Usually first 3/12 of abstinence significant improvement in liver function and avoidance of liver transplant
- Period of abstinence opportunity to asses patient compliance





Non alcoholic fatty liver disease/NAFLD/NASH

Def. :accumulation of fatty acid content >5% of liver weight

-Fastest growing indications for liver transplantation in the last 20years
-Most common cause of chronic liver disease in western world(17-30%) and only 2-4%World widen and leading indication for liver transplant in USA
-Identified on imaging in 20-33% of adult plus 3-16% potential liver donor
-Usually diagnosed between 40-50years of age
-HCC with NASH increased 7,7 fold and usually non cirrhotic and not included in screening programs , large tumour, difficult to screen with ultrasound due obesity as hence diagnosed late

work up in pretransplant and post transplant

-Obesity BMI
-Hypertension
-Diabetes
-Dyslipidaemia

Morbid obesity
-increase risk of infection complication
-increase risk of prolonged ICU and hospital stay
-usually have sarcopaenia and myosteatosis
-need weight loss required for liver transplant candidates

Management

-diet
-physical exercise
-pharmacology(GLP-1 analogue, SGLT-2,DPP4 inhibitors

LEAN TRIAL -Liraglutide resolution of NASH in 39% pts

-bariatric surgery
(weight loss to improve fibrosis, maybe at same time or post liver transplant)
Sleeve gastrectomy, gastric banding or gastric bypass
Diabetes mellitus
-prevalence is 32-66% among patient with NAFLD
-pre LT DM associated with (increase risk of post LT infection, cardiovascular complications, longer hospital stay, decrease long term graft survival)
-preLT diabetes treatment (side effects, risk hypoglycaemia and associated risk in acute kidney injury
-NAFLD Child C only therapy is insulin agent
-Hba1c may be too low due to splenomegaly and anaemia

Post liver transplantation in NAFLD

-Peri surgical complications increase infection rates
-Long term (cardiovascular event and malignancy)
-Incidence of post transplant NASH significant higher
-Prevalence of diabetes is 31-38%
-New onset diabetes is 13-28% in the first 3years after surgery
-Diabetes affect prognosis of liver transplant recipients with higher 10year mortality/infection rates and CVS events hence euglycaemia is primary goal in post liver transplant

Risk of post transplant diabetes mellitus

-Male
-Family history
-Hepatitis C

Management of patients with NAFLD post transplant

-Dm , morbid obesity and CVS disease present frequently in patients with NAFLD who are candidates for LT
-Need presurgical risk stratification to improve outcome after liver transplantation
-Immunosuppressant will increase metabolic complication and cvs events with early post transplant complications
-Long term malignancy and cardiac events

2.CARDIOVASCULAR ASSESSMENT

-All liver transplant exclude underlying heart disease
-Cirrhosis associated with increase cardiac output and latent cardiac dysfunction
-Latent cardiac dysfunction (decrease cardiac contractility with both systolic and diastolic dysfunction =cirrhotic cardiomyopathy

Exclude
-Coronary artery disease
-Cirrhotic Cardiomyopathy
Work up
-ECG
-ECHO
-CardioPulmonary Exercise Test

(>50years and multiple cardiovascular risk) to uncover asymptomatic Ischaemic heart disease)
Need to reach target heart rate
Not Pharmacological Stress test
Coronary artery disease be treated prior liver transplantation

a) Cirrhotic Cardiomyopathy
-Occurs in 50% of patients with cirrhosis regardless of aetiology
-Additive in alcoholic and hemochromatosis
-Under recognised condition
-Can reverse post LT
-There is direct correlation between severity of liver disease
-Unrecognised condition with poor prognosis

Characteristics

-Diastolic and systolic dysfunction
-Hyper dynamic circulatory state
-Impaired cardiac response to stress
-Various electro physiological abnormalities (QT prolongation)

Epidemiology
-Asymptomatic with near normal cardiac function except during stress
-Undergoing transplantation 50% have observed to develop signs of cardiac dysfunction within perioperative period
-There is 7-21% mortality from heart failure in months post transplant

Who are at risk
-Male gender
->50years
-Alcoholic and hemochromatosis cirrhosis

Pathophysiology
Cirrhosis
-Effective central hypovolaemia (functional hypovolaemia)despite absolute volume overload

- Splanchnic vasodilation (nitric oxide , endocannabinoid)
- Decrease systemic vascular resistance compensating for cardiac dysfunction and produces asymptomatic clinical picture at rest

Renin Aldosterone System activation and Sympathetix nervous system with down regulation of B adrenergic receptors in plasma membrane with resultant autonomic dysfunction

Cardiac dysfunction due
-Alteration in cell membrane composition
-Ion channel defects
-Autonomic dysfunction
-Overproduction of cardiodepressant factors
-Decrease in L type calcium channel and K+ channel with increase action potential leading to QT prolongation
-Na/Ca2+channel dysregulation with massive Ca influx in cells that stimulate cardiomyocyte apoptosis
(Impaired Myocyte relaxation , alterations in collagen and Titin configuration)
Leads to eccentric left ventricular hyper trophy and diastolic /systolic dysfunction

HISTOLOGY of CCM
-Fibrosis
-Subendocardial oedema
-Vacuolation of nucleus and cytoplasm

CLINICAL EXAMINATION
-Unremarkable but Physiological /pharmacological stress test signs of CCF may appear

EVALUATION FOR CCM
CXR

- Normal or slight cardiomegaly and pulmonary oedema
ECG
- QT prolongation could be the 1st sign of CCM, but can vary between daytime and night time due to diurnal variation in autonomic nervous system and circulatory system
ECHO
-Diastolic and systolic dysfunction

Diagnostic criteria 2005 World Congress in Montreal

- ECG QT prolongation
- Evidence of systolic dysfunction as evidence by blunted increase in cardiac output with physiologic or pharmacological stimulation
- LV ejection fraction <55%
- Evidence of diastolic dysfunction (Mitral deceleration time >200mseconds, EA ratio <1
- Isovolumetric Relaxation Time (IVRT) > 80ms
- Other various supportive criteria (enlarged left atrium, increase LV wall thickness
- High Pro BNP and Troponin I

MANAGEMENT

1.Standard medical therapy for management of heart failure

- ACE or ARB

(decrease morbidity and mortality in heart failure but not in ChildPugh B or C as might exacerbate systemic vasodilation and increase risk of hepatorenal syndrome

- Loop diuretic +thiazides for hypervolaemia
- Aldosterone receptor antagonist

(Improve hemodynamic in patient with CCM by blocking RAAS

- B blocker

(portal pressure and decrease variceal bleeding)

Carvedilol decrease portal pressure ,decrease variceal bleeding and decrease QT prolongation

2.Liver transplantation

- LT cornerstone of treatment and definitive
- Improve systolic and diastolic dysfunction
- Reverse QT prolongation in 50%of patients
- Cardiac benefits observed within 3-12/12 post LT

1. RESPIRATORY FUNCTION ASSESSMENT

a)HEPATOPULMONARY SYNDROME

Def.: decrease arterial O2 saturation due dilated pulmonary vasculature in the presence of advanced liver disease or portal hypertension

- Normal pulmonary size of pulmonary vasculature is 8-15um but in HPS dilated ranging from 15-500um
- Dilatation decrease transit time for blood cells with large amount of blood passing through pulmonary vasculature without undergoing gas exchange leading to impaired ventilation
- Leads ventilation perfusion mismatch leading to Increase Alveolar-Arterial Gradient with subsequence Hypoxaemia
- Pulmonary vasculature dilatation more in the lung bases hence Platypnoea and orthodeoxia associated
- Severity of HPS not correlate with severity liver disease
- 10-17% with cirrhosis

Pathophysiology

- Imbalance in pulmonary vasoconstriction and vasodilation
- Stimulation of pulmonary endothelial nitric oxide synthetase leading to increased Nitric oxide production hence vasodilation
- Also VEGF production with angiogenesis in pulmonary vasculature

Vasodilation and angiogenesis leads to AV shunt formation within pulmonary vasculature

Diagnostic criteria

-PaO2 level <80mmHg while on room air
-Alveolar-arterial O2gradient (A-aO2) > 15mmHg while at rest breathing room air
-Pulmonary vascular dilatation shown on positive contrast enhanced Echo
-Radioactive lung perfusion scanning showing Brain-shunt fraction > 6%
-patient with portal hypertension with or without cirrhosis

Severity assessment of HPS

Mild HPS
-PaO2>80mmHg with A-arterial O2>15mmHg while breathing room air

Moderate HPS
-PaO2 <80mmHg but >60mmHg with A-aO2 Gradient >15mmHg Room Air

Severe HPS
-PaO2<60mmHg but >50mmHg with A-aO2 Gradient >15mmHg

Very Severe HPS
-PaO2<50mmHg / A-aO2 >15mmHg at room air
Or
-PaO2 <300mmHg on 100%O2

Classification of HPS

I)Type 1 HPS

-dilatation of pulmonary vasculature at precapillary levels near gas exchange unit of the lung

-supplemental O2 improve or increase PaO2 level

II)Type 2 HPS

-Larger dilatation of vessel cause AV shunt from gas unit

-Supplemental O2 not improve PaO2

CLINICAL PRESENTATION

-Asymptomatic in the early stages

-Dyspnoea in the setting of liver disease

-Platypnoea(worsening of dyspnoea moving from supine to upright position)

-Orthodeoxia(decrease of PaO2 >5% or 4mmHg when moving from supine to upright position

-Digital clubbing

-Diffuse telangiectasia

-Cyanosis

EVALUATION FOR HPS

a)Pulse Oxymeter screening with Saturation <96% or PaO2<70mmHg

-Confirmation with ABG

PaO2 <80mmHg

b) CXR

-Normal or increase bibasilar nodular opacity coinciding with increase pulmonary dilatation

-Helpful to exclude coexisting pulmonary pathology

c)contrast enhanced ECho with agitated saline
(Gold standard for diagnosing pulmonary vascular dilatation)
Normal saline agitated to generate micro bubble>10micrometer in diameter
Normal saline injected peripheral vein in the arm with simultaneous trans thoracic echo performed

Micro bubbles are trapped in pulmonary circulation and absorbed in alveoli
Pulmonary dilatation/AV shunts micro bubbles evade the pulmonary capture and reach left atria seen by TTE in left atrial chamber
Appearance of micro bubbles in left atria between 4 and 6 cardiac cycle indicates pulmonary vasodilation
If appears before the 3cardiac cycle suggest intracardiac shunt
d)Transeophageal Echo
Superior to TTE but invasive
Concerns of oesophageal varices

e)Radioactive Lung Perfusion Scanning
-Not as sensitive as contrast enhanced Echo
-Radiolabelled albumin aggregates of 20um in diameter are given IV into peripheral vein
-Normally radiolabelled albumin of 20um are trapped in the pulmonary circulation and scintigraphy reveal near complete uptake in the lung.
-Intrapulmonary shunting (some fraction of albumin pass through the pulmonary vasculature into systemic circulation and scintigraphy shows uptake in other organs in addition to the lung and allows calculation of shunt fraction
Brain Shunt fraction > 6% is significant

f)Pulmonary angiogram
-Help distinguish Type 1(precappilary dilatation from Type 2(large shunts)
-Invasive , expensive and less sensitive than contrast enhanced Echo
g) Pulmonary function Test
-Decrease diffusion capacity for carbon monoxide DLCO

TREATMENT
a)O2 supplement if severe until definitive treatment
b)Liver transplantation
-Only established treatment long term survival benefit for HPS
-Liver transplantation before severe hypoxaemia <50mmHg
-PaO2 and A-aO2 reverse rapidly after transplant within 6/12
-Intrapulmonary shunt reverse may take longer than 6/12
-DLCO improves
c) TIPS
-Worsens the the Intrapulmonary vasodilation and shunt with worsening Hypoxia
-Risk of hepatic encephalopathy

Differential diagnosis
-Pneumonia
-Pneumonitis
-Pleural effusion
-Recurrent pulmonary emboli
-Atelectasis

-COPD
-ASD
-Atriovenous malformation
-Porto pulmonary hypertension

PROGNOSIS
-Higher mortality
-Associated with poor quality of life
-Average life span is 10 months
-HPS mortality rate increases with severity of liver disease with worse prognosis inpatient with severe disease
-post liver transplant survival is decrease in patient with severe HPS

b)PORTO-PULMONARY HYPERTENSION

Def: pulmonary arterial hypertension associated with portal hypertension
-Prevalence of 6%
-Lack of hepatic clearance of vasoactive substance with resultant elevation in pulmonary pressure with R ventricular dysfunction
-Occurs in 90% cirrhotic portal hypertension and 10% noncirrhotic portal hypertension
-Pulmonary hypertension not related to severity of liver disease or severity of portal hypertension
-Worsens prognosis of liver transplant
-Has negative impact on liver transplant success

Risk
-Female
-Autoimmune disease

Diagnostic criteria of POPH
-Portal hypertension 15mmHg
-Mean Pulmonary arterial pressure >25mmHg

Clinical presentation
-Asymptomatic
-Symptomatic (fatigue , oedema and sever dyspnoea
-Need to look for porto pulmonary hypertension in every LT candidate as many may be asymptomatic

Grading of portò pulmonary hypertension

Mild POPH
mPAP >25mmgH but < 35mmHg

Moderate POPH
-mPAP>35mmHg but <45mmHg
Severe POPH
-mPAP >45mmHfg

PRETRANSPLANT WORK UP AND TREATMENT
-Target pulmonary pressure <35mmHg with vasodilator

I)Trans thoracic echo as a screen
-Highly sensitive and noninvasive
-Pulmonary Artery Systolic Pressure >50mmHg

II)Trans esophageal echo
-Rule out other cause of elevated pulmonary artery pressure

III)R heart catheterisation
-If Pulmonary Artery Systolic Pressure >50mmHg
-Ascertain diagnosis of POPH
-Prognosticate and grade POPH

Differential diagnosis
-High output state of cirrhosis
-Cirrhotic cardiomyopathy
-Hemodialysis as a bridge to transplant esp those poor candidates for TIPS and not responding to vasoconstriction

TREATMENT

Moderate Severe Pulmonary hypertension with mPAP >35 mmHg and PVR >240dyn.s.cm3

-Start pulmonary vasodilator and asses response to treatment through TTE and RHC every 3/12 and mPAP >35mmHg Liver transplant is contraindicated

-If response to mPAP <35mmHg and PVR <400dyn.s.cm3, and R ventricle is preserved then Meld exception points assigned and liver transplant considered

LIVER TRANSPLANTATION IN POPH

Intra operative risk of increase mPAP

-R heart failure leading graft failure

Precipitants of POPH

-High level of ventilation pressure

-High Peep

-Hypoxia

-Acidosis

-Hypercapnoea

4.RENAL DYSFUNCTION AND CIRRHOSIS

-Cirrhosis patient with renal failure have 7fold increase risk of death and 50% die within 1month

-Assess renal function essential in evaluating patient for liver transplantation

a) Hepato renal Syndrome
-Serious complication of cirrhosis
-Associated with high morbidity and mortality
-Characteristics feature of functional circulatory changes in the kidneys that overpowers physiological compensatory Mechanisms leading to decrease glomerular filtration

Dx

-decrease in kidney function
-lack evidence of intrinsic kidney disease(no haematuria, no proteinuria , normal kidney imaging, normal histology
-cirrhotic setting

Functional changes in renal circulation and potentially reverse with liver transplantation
i)Type 1 HRS AKI
-Acute impairment of kidney function
-Rapid and progressive decline in renal function
-Doubling of serum creatinine to atleast >2,5 or decline creatinine clearance by >50% or more over 2week period
-Urine output <500ml/day with normal urine sediment
-Low urinary Na excretion
-Exclude (prerenal, nephrotoxic drugs , obstructive nephropathy and renal parenchymal disease)
-Has poor prognosis
-Average survival is 2 weeks
Hepatorenal Syndrome Type 1
Rapid rise in the serum creatinine level
Doubling of the initial serum creatinine level greater than 2.5mg/dl in less than 2 weeks
Prognosis: poor; usually occurs secondary to precipitating factors including SBP, gastrointestinal bleeding, large voume paracentesis
Inpatient-ICU
● Treatment: Terlipressin, Norepinephrine, Midodrine, Ocreotide
Transplant

ii) Type 2 HRS CKD
-less severe kidney injury
-diuretic resistant ascites

Hepatorenal Syndrome Type 2
Gradual increase in the serum creatinine level

- Slow rise above 1.5 mg/dl
- Associated with diuretic resistant refractory ascites
- Outpatient close follow up
- Treatment: Midodrine, Ocretotide
- Transplant

Prognosis: 6 months without treatment
Prognosis: 10 percent survival at 90 days

Pathophysiology of HRS

- Splanchnic and systemic vasodilation
- Relative central hypovolaemia
- Activation of RAAS system /sympathetic/Vasopressin release
- Increase vasoconstriction leads hypo perfusion and renal dysfunction

Precipitants

- GI bleeding
- Large volume paracentesis without plasma expansion
- Spontaneous bacterial peritonitis

TREATMENT/MANAGEMENT OF HRS

a) Medical

i. Establish euvolaemia

- Stop all nephrotic drugs
- Direct treatment at splanchnic vasodilation by vasoconstriction form of terlipressin
- Albumin infusion to improve renal perfusion

Terlipressin and albumin for type 1 HRS

- Octreotide /Noradrenaline

ii) Treat spontaneous bacterial peritonitis with iv antibiotics

iii) Renal replacement therapy

- MARS (molecular adsorbent recirculating system) aimed at removing substance causing vasodilation like nitric oxide and TNF

b) TIPS (shunt to decrease portal pressure and increase systemic venous return-decrease arterial hypo perfusion-decrease RAAS and decrease Sympathetic nervous system

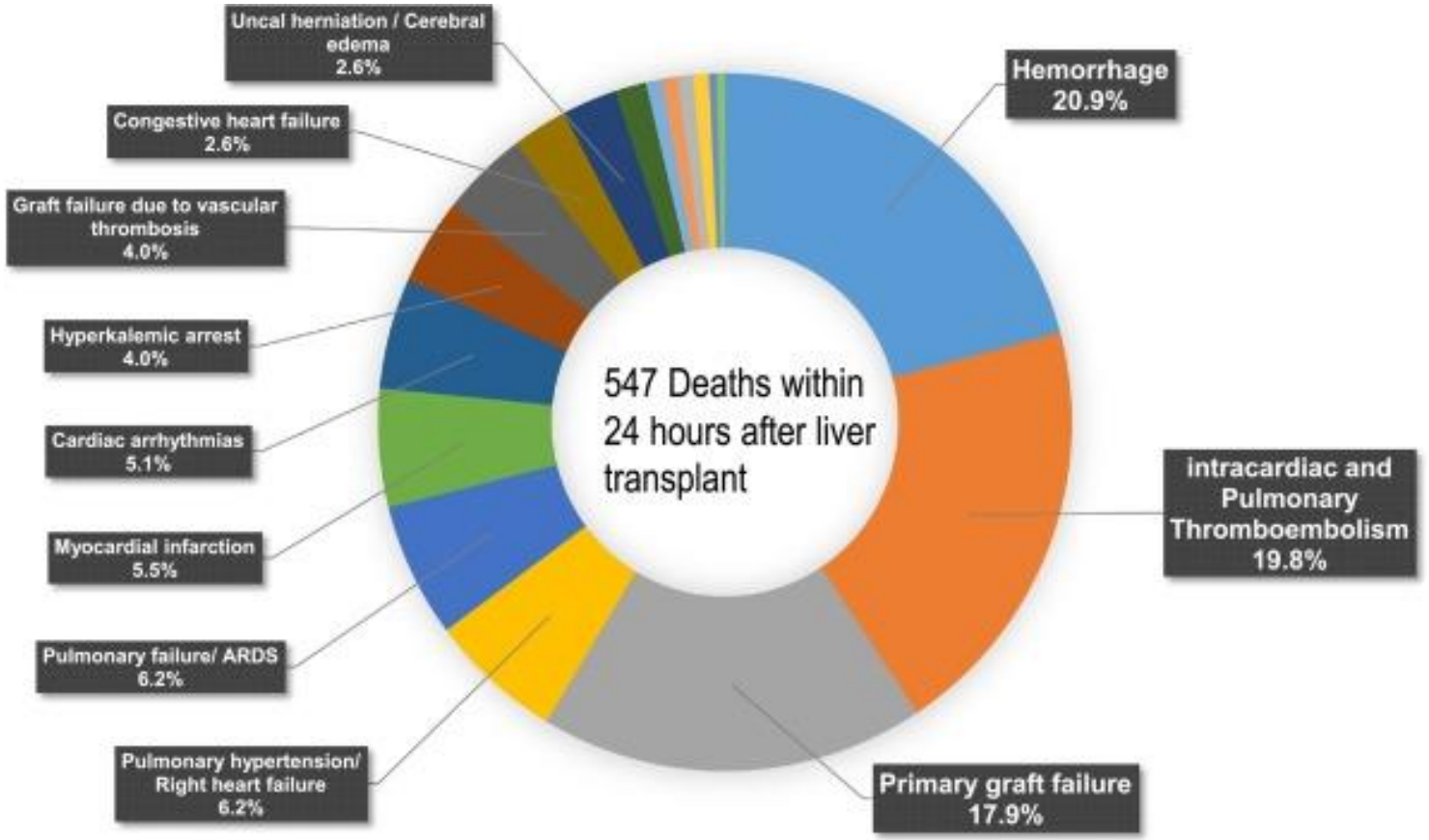
c) Liver transplantation

d) Liver Kidney transplantation

- GFR <30
- HRS requiring renal replacement therapy for 8-12 weeks
- Kidney biopsy showing >30% fibrosis and glomerular nephritis

POST LIVER TRANSPLANTATION first Week

-Most hospitalisation 7-14 days (1-2 days ICU 3-14 days ward and discharge)
-Takes around 6/12 recuperate



Predictors of post transplant outcome

Donor -recipient parameters

a) Donor
   - Advanced age
   - High body mass index
   - Degree of hepatic steatosis
   - Base line liver function
   - Cause of death
   - Length of hospitalisation
   - Use of vasopressors
   - Whole graft or split graft
   - Cold ischemia time

b) Recipient
   - Age
   - HCV status
   - Urgent status
   - Renal dysfunction
   - Ventilatory requirement

2. Operation related requirements
    - Cold ischemia for >12hrs
    - Warm Ischaemic > 45 minutes
    - Amount of blood loss
    - Blood and blood product administration
    - Lack of immediate bile production

3. Post procedure indications
    - Elevated transaminases
    - Serum bilirubin
    - PT level
    - Serum creatinine

Liver transplantation(1 year allograft and patient survival 85% and 90%) with 5 year survival of 75% allograft and 80% patient

Care of transplanted organ

- Monitoring and early recognition of graft dysfunction / organ rejection
- Initiate immunosuppressant and monitoring compliance and side effects
- Manage surgical complications
- Support transplant recipient and care giver

Monitoring post liver transplant

- Vascular patency -Doppler ultrasound
- Rejection-suspect liver biopsy
- Infection
- Bleeding
- Cardiovascular
- Pulmonary
- Metabolic syndrome
- Diabetes
- Hyperlipidaemia
- Osteoporosis
- Recurrence of primary disease

Immunosuppressant to prevent rejection

Calcineurin Inhibitors (CINs)

a) Tacrolimus (Prograf)
b) Cyclosporine
c) MMF mycophenolate mofetil/Cellcept
d) Azathioprine
e) Prednisone

- Need regular blood sample check level of drugs
- Dose altered until right balance
- If level too low (rejection risk) if too high (toxicity more side effects)

Critical in the 1st 3/12 after transplant

- Drug level
- Drug toxicity
- Rejection of new liver
- Infection of graft

Common infection associated with transplant

1. Viral infection and fungal
    a) CMV infection
        - Risk highest in first month after transplant
        - Present with fever , fatigue, aching joints and headache
    b) Herpes simple virus
        - Skins
        - Eyes
        - Lungs
    c) Herpes zoster
        - Hip
        - chest
    d) Varicella
    e) Candida
        - Mouth

- Respiratory
- Genito urinary
- Eyes

POST LIVER TRANSPLANT MEDICAL COMPLICATION

LIVER transplant effective therapeutic modality for
- Irreversible acute liver failure
- Irreversible chronic liver failure

Outcome improved in the last 2 decades
- Advances in perioperative technique
- Improvement in immunosuppression
- Effective post operative care

Complication are common occurring early or long term
survival rate of 90-95% in 1year and 75% at 5years
Postoperative

a) Hypotension
    - Hypoxi
    - Ischemia
    - Hepatotoxic drugs
b) Donor related factors -hepatic steatosis
c) Surgical related

- Intraoperative or post operative haemorrhage
- Vascular complication
- Biliary complication

d) Immune response related
    - Rejection

Outcome depends
- Patient pre operative state
- Quality of donated liver
- Complexity of surgery

Immediate Post transplant complication

1.Graft dysfunction
- Primary non-union
- Primary poor function
- Acute cellular rejection
- Recurrent viral hepatitis
- Drug hepatotoxicity

2.Surgical complications
    - Prevalence of 20%

a) post operative haemorrhage
    - variable prevalence of around 20%

Risk

- Pre-existing coagulopathy
- Significant haemorrhage intraoperative
- Poor synthetic function

Diagnosed 48hrs post transplant

- Haemorrhagic abdominal drainage
- Hemodynamic instability
- Decrease haemoglobin

Subside with conservative treatment
Re operation needed in 10-15% cases
Cause found in only 50% cases

b) Vascular complication

i) Hepatic artery thrombus

- Prevalence 1.5-25%

risk factors

- Poor arterial flow
- Stenosis of anastomoses
- Hypercoaguable state
- Increase sinusoidal resistance
- Preservation injury

Complication

- Ischaemic/necrosis of graft
- Ischaemic billiopathy(biliary stenosis

Diagnosis

- Doppler ultrasound
- Seletive arteriogram

Treatment

- acute thrombolysis or arterial thrombectomy by interventional radiology or surgical intervention
- bilioenteric bypass
- Urgent re transplantation

50-70% patients with hepatic arterial thrombosis need re transplantation

ii) Portal vein thrombosis

- Infrequent
- Prevalence of 2-3%

Risk

- Splenectomy
- Prior portal hypertension surgery

Complication

- Acutely with hepatic failure
- Late onset portal hypertension

Rule out stenosis of venous anastomoses

- Per cutaneous dilatation by angiography
- Surgical resection and direct anastomoses with /without venous graft

iii) Hepatic venous obstruction

c) Biliary tract complication

- Biliary leakage /fistula
- Biliary stricture

Clinical presentation

- Lack of bile formation
- Increase WCC
- Increase cholestatic enzyme

Medical complication

a) Hemodynamic complications

i) Arterial hypertension

- Immunosuppressive drugs
- Intense pain
- Hypervolaemia(excessive fluid replacement)

Treatment

- Calcium channel blocker
- Diuretic therapy

ii) Electrolyte imbalance

- Na/k/Ca/Mg

Due to hepatic re perfusion

Complicate

- cardiac arrhythmia (bradycardia/SVT

Exclude

- Acidosis and correct
- Renal failure
- Graft failure

b) Respiratory complications

- Abdominal surgery
- Decrease diaphragmatic mobility
- Ascites
- Pleural leakage
- Interstitial oedema
- Emboli

Decrease ventilation capacity and complicate removal of mechanical ventilation

c) Renal dysfunction

Risk

- Pre existing renal dysfunction
- Peri operative haemorrhage
- Hypotension

- Use of nephrotoxic drugs
- Sepsis
- State of shock
- Graft dysfunction

Defined by increase in basal creatinine by >50%or creatinine level above 2-3mg/dl (176 -265)

Clinical presentation
- Oliguria
- Electrolytes imbalance
- Oedema
- Acid/base disturbance
- Increase creatinine level 2nd and 4th day post operation

Consider
- Euvolaemia
- Use of diuretics
- Dopamine and noradrenaline
- Dialysis

d) Neurological dysfunction

Intracranial haemorrhage
- Coagulopathy
- Hypertension

Anoxic ischaemic encephalopathy
- Haemorrhage

- Hypoxia

Convulsions

- Antibiotics
- Cyclosporine
- Tacrolimus
- Drug toxicity
- Pre-existing like alcohol/diabetes

e) Allograft dysfunction

Evidence of graft well functioning

- Normal acid base status
- Normal ammonia
- Absence of encephalopathy
- Good biliary production
- decrease transaminases
- Increase factor V
- Increase in platelets count

i) Early graft dysfunction

- surgical complications
  - Vascular (hepatic artery or portal venous thrombosis/stenosis
  - Biliary (fistula or leakage)
- Drug related liver toxicity
- Infectious complications (CMV , bacterial
- Graft itself

❖ **Primary graft dysfunction/malfunction /failure**

Def.: Poor liver function to maintain the individual's life leading to either death of the patient or re transplantation occurring during the 1st 7 days post operation

- Graft failure is a serious situation
- Characteristic of primary graft failure/immediate non functioning of liver
- Scanty or no bile elimination
- Elevated ammonia
- Coagulopathy (factor V <20%
- Hepatic encephalopathy
- Elevated transaminases AST>5000
- Lactic acidosis that cannot be corrected
- HistoHogy evidence of Ischaemic hepatic necrosis

Predisposing to primary graft failure

- Advanced age
- Cold Ischaemic time of graft
- Reperfusion damage
- Release of intestinal endotoxins
- Hemodynamic instability
- Drug related liver toxicity
- Unknown

How do you improve graft functioning post transplant

- Use prostaglandins in the 1st hours to improve micro circulation of the liver graft

If all fails after 24-48hrs with no regression of clinical situation then consider re transplantation to avoid multi organ failure

- NB

- graft rejection

Diff diagnosis of acute rejection

- Viral hepatitis (CMV,EBV , recurrent Hep B and C
- Calcineurin inhibitors toxicity

Rejection can be diagnosed with liver biopsy if unclear

Rejection treatment

- Iv corticosteroids
- Antithymocytes when steroids ineffective in 10-20% cases
- Re transplantation

4. Organ dysfunction

- Renal
- Pulmonary
- Cardiac
- Neurologic

Long term complication

1. Prolonged immunosuppression therapy
- Diabetes
- Hypertension
- Organ toxicity
- Denovo neoplasm

2. Recurrence of original disease

<u>Complication of liver transplantation</u>

a) Rejection
- Liver allograft less rejection than other allograft for unknown reasons

Risk for rejection

- Old donor age
- Younger recipient
- Greater HLA mismatch
- Longer Ischaemic time
- Autoimmune disorder

c) Primary non function

- Never function and need re transplant in 1-5% cases

d) Mechanical biliary dysfunction

- Ischaemic anastomosis stricture
- Bile leakage
- Ductal obstruction

e) Portal vein thrombosis

- In <5% cases

f) Hepatic artery thrombosis

- 3-5% cases
- Common in small children or recipient of split graft

g) Hepatic artery mycotic aneurysm and rupture

Prognosis of liver transplantation

- At 1 year survival is 90% and 82% of graft
- Survival better for those who had chronic than acute liver failure

death in 1 year due to

- Recurrent disorder (cancer, Nash , hepatitis B and C , autoimmune) than post transplant complication .
- Hep C recurrence may lead to cirrhosis in 15 -30%within 5 years
- Autoimmune (PBC and PSC and autoimmune hepatitis recurs in 20-30% within 5 years