Note: CRE status must not compromise patient management and CRE-positive patients shall not be refused admission to any HCF or RCF.

The transferring facility shall notify the receiving HCF or RCF prior to transfer of a CRE-positive patient.

Patient Discharge

Patient discharge All CRE-positive patients are to be provided with information on the risk of transmission, the importance of notifying health care providers of their status, and be made aware of the possible lifelong carriage of CRE.

Environmental Cleaning of CRE-Positive Patient Rooms

Note: Persistence of environmental reservoirs of pathogens is usually related to a failure to follow recommended cleaning procedures rather than specific cleaning and disinfectant agents. For effective environmental disinfection, physical cleaning with detergent and thorough application of the disinfectant, which allows for adequate contact time with the surfaces, is required. Physical cleaning is very important, whether a two-step procedure (detergent then disinfectant) or a 1-step (detergent plus disinfectant) in 1 product is employed.
Metabolic Liver Disease
Presentation

- Infantile Cholestasis
- Acute liver failure
- Neonatal Ascites
- Hepatomegaly/splenomegaly
- Hyperammonemina/Acidosis
Metabolic Liver Disease

Common Features

- Positive family history
- Unexplained neonatal deaths/multiple miscarriages
- Consanguinity
- Recurrent episodes of unexplained vomiting, encephalopathy
- Developmental delay/regression
- Dysmorphism
Metabolic Liver Disease
Clinical Clues

- **Coarse facies-**
  - Gangliosidosis, MPS, Sialidosis

- **Macroglossia-**
  - GM1 Gangliosidosis

- **Diarrhea-**
  - Wolman’s Disease, Cystic fibrosis

- **Mild Lymphadenopathy-**
  - Wolman’s Disease, Gaucher’s Disease

- **Upward gaze palsy, opisthotonous-**
  - Gaucher’s Disease

- **Cherry red spot-**
  - Niemann-Pick, GM1 Gangliosidosis
Metabolic Liver Disease
Clinical Clues
abnormal odor

Sweaty feet
- Glutaric acidemia, Isovaleric acidemia
- Rancid, fishy, or cabbage like
- Tyrosinemia
Zellweger
Metabolic Liver Disease Radiologic Clues

- Adrenal Calcification
  - Wolman’s Disease
- Stippled Epiphysis
  - Zellweger’s Syndrome, GM1 Gangliosidosis
- Rickets
  - Tyrosinemia
Metabolic Liver Disease

Jaundice in Neonate

- Unconjugated Jaundice
  - Crigler Najjar Syndrome
  - Galactosemia, hypothyroidism initially
  - HLH
Metabolic Liver Disease
Infantile Cholestasis

- Galactosemia
- Tyrosinemia
- Hypo/hyperthyroidism
- Hypopituitarism (SOD)
- Bile acid defects
- Gaucher’s disease
- Fructosemia
- NN hemochromatosis
- Alpha-1antitrypsin def
- PFIC
- Cystic fibrosis
- HLH
- Peroxisomal disorders
- Niemann-Pick Band C
- Wolman’s Disease
- Organic acidemia
Metabolic Liver Disease

Infantile cholestasis  *Investigations*

- Blood sugar q 6 hrs
- Lactate, pyruvate
- Blood gas
- Uric acid
- Ammonia
- CPK
- Transferrin
  - Electrophoresis
- Save Blood sample
- **Urinary Inv**
  - Reducing sub
  - amino acids
  - Organic acids
  - Bile acids
  - Electrolytes
Metabolic Liver Disease

Infantile Cholestasis  *Specific Investigations*

- Alpha-1 antitrypsin def
- Galactosemia
- Tyrosinemia
- Bile acid defects
- Cystic fibrosis
- Hypothyroidism
- Hypopituitarism

- Phenotype (ZZ) level?
- Gal-1 PUT levels
- Urine succinyl acetone
- Serum and urine bile acid spectroscopy
- IRT/Sweat test
- TSH and T4
- Cortisol/ synecchin
Metabolic Liver Disease

Infantile cholestasis  *Tests on White blood cells or cultured fibroblats*

- Wolman’s disease
- Gaucher’s disease
- Sialidosis type II
- GM 1 Gangliosidosis
- MPS VII

- Acid lipase levels
- B-glucocerebrosidase
- Neuraminidase levels
- Acid B-galactosidase
- B-glucuronidase def
Liver Biopsy
Metabolic Liver Disease

Histologic Clues Liver

- **PAS +/diastase resistant granules**
  - Alpha-1-antitrypsin def, GSD 4, Afibrinoginemia

- **Iron**
  - Zellweger’s Syndrome, Neonatal hemochromatosis

- **Fatty change**
  - Non specific but important indicator

- **Glycogen and plant like cells**
  - Glycogen Storage Disease

- **Copper**
  - Wilson’s Disease, other copper disorders but could indicate chronic cholestasis
Metabolic Liver Disease

Histologic Clues

- Skin Biopsy
  - Laffora body disease, GM1 Gangliosidosis

- Bone Marrow
  - Wolman’s Disease, Gaucher’s Disease, Niemann-Pick type C, Hemophagocytic Lymphohistiocytosis
Tissue Handling

- Liver Biopsy
  - Snap freeze
  - EM
  - Discuss with lab special requirements for enzyme studies

- Skin Fibroblast culture
A.D

- SVD at 37+5 wks, B.wt. - 3.2 kg
- Physiological jaundice noted at D_2
- Reviewed at local hospital on D_{18}
  - yellow dark urine & pigmented stool
  - wt. Loss
  - Investigated and
A.D

- Mildly jaundiced
- Liver : 3 cm palpable at MCL
- No palpable spleen
- No other s/o liver disease
- Conjugated hyperbilirubinemia work up done
A.D

- FBC, INR – normal
- U&E’s – normal
- Bili – 129/67
- AST – 219
- GGT – 98
- ALP – 518
- TP/Alb – 59/39
- Lactate – 2.5
- CPK – 40
- TSH/Cortisol – normal
- AFP – 114,700
- Gal-1-PUT – normal
- A-1-AT – normal
- UOA/UAA – normal
- Urine bile acid – normal
A.D

- USS abdomen:
  - Homogenous liver parenchyma
  - No duct dilatation
  - Normal vessels
  - Spleen normal in size

- Liver Biopsy: Idiopathic neonatal giant cell hepatitis
A.D

- Regular follow up – persistent abnormal LFT’s
- 6 month follow up:
  - Cleared jaundiced
  - Development normal
  - Hepatosplenomegaly
A.D

- BMA: Cellular active marrow. Some suspicious macrophages suggesting storage cells.
- Skin biopsy for fibroblast culture:

  Cholesterol esterification defect (Niemann-Pick C disease)
- 3 wks old boy, mild dysmorphism
- Fits
- Acidosis
- Conjugated jaundice, Low GGT
- Hypotonia
- Incomplete extension of Rt knee and elbow
- Liver Biopsy-Giant cell hepatitis
ARC COMPLEX

Arthrogryposis
Renal
Cholestasis
A.B

- 13 yr old boy
- H/O intermittent rectal bleeding and nose bleeds for nearly 2 yrs
  - Abnormal AST, ALP but Bilirubin, Albumin and clotting normal
  - AAB, A-1-AT, Hepatitis serology : normal
  - Normal colonoscopy and USScan
A.B

- **USScan abdomen**:  
  - Homogenous liver parenchyma with uniformly ↑ reflectivity s/o fatty changes  
  - Biliary tree normal  
  - Portal vein patent  
  - Spleen: 12 cm (upper limit of normal)
A.B

- Managed as NASH locally
  - Ht: 50th %ile, Wt: >90th %ile
  - No s/o chronic liver disease
  - Hepatosplenomegaly
  - Chronic liver disease work up completed
A.B

- Cearuloplasmin : 0
- Pre-penicillamine urine Cu: 3.1 $\mu$mol/d
  - Post-penicillamine urine Cu: 21.7 $\mu$mol/d
- Liver copper : 525 $\mu$g/gm of dry liver

Diagnosis : Wilson’s disease
Glycogen Storage Disease

- Doll like face, Big belly
- Sweating, irritability, sweet craving
- Hepatomegaly
- No Jaundice
- Usually no splenomegaly (type IV)
- Elevated Cholesterol/TG, Uric acid, Lactate
- Liver enzymes not very elevated
Distribution of various types of glycogenoses

Type I
Type III
Type IV
Type VI

USA
European
ALF as presentation

- Neonatal haemochromatosis
- Galactosaemia
- Tyrosinaemia
- Mitochondrial cytopathies
- Fructosaemia
- Fatty acid oxidation defect
- Bile salt synthetic disorders?
- Urea cycle defects
- Wilson’s disease
Neonatal haemochromatosis

- Hepatitis/liver failure within days of birth
- IUGR, megaplacenta, oligohydramnios
- Prognosis generally very poor
- 80% recurrence
- Survival currently about 65% with liver transplantation
Neonatal Haemochromatosis

17 infants < 3 months of age
10 male, 5 - 84 days (median 33)
Inborn errors of bile acid synthesis

- Deficiencies of:
  - Hydroxy-delta5-C27-dehydrogenase-isomerase
  - Delta4-3oxosteroid-5beta-reductase
  - ?others

- Severe progressive intrahepatic cholestasis, low GGT, no pruritus, low and abnormal plasma bile salts

- Respond well to exogenous bile acid therapy
Fatty acid oxidation Defects

- Maternal illness in pregnancy
- Intercurrent viral illness
- Hypoketotic hypoglycaemia
- Encephalopathy
- Cardiomyopathy
- Myopathy
- Hepatomegaly
- Abnormal Liver enzymes
- Liver failure?
**Metabolic Liver Disease presenting as ALF**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Coagulopathy</th>
<th>Encephalopathy</th>
<th>Tubulopathy</th>
<th>Age Specific features</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid Oxidation defects</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>&lt;10 yrs ↓ketone, ↓gluc, ↓Tone</td>
</tr>
<tr>
<td>Zellweger</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Oragnic acid Fibroblast fat oxi, VLCFA</td>
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<tr>
<td>CDGS 1A</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>_</td>
<td>Dysmor Fits, ↓Tone</td>
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<tr>
<td>CDGS 1B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>_</td>
<td>Phosphomannomulase, Isoelec focus, Phosphomannose isomerase</td>
</tr>
</tbody>
</table>
# Metabolic Liver Disease presenting as ALF

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<th>Jaundice</th>
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<th>Age</th>
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<th>Diagnostic test</th>
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<tbody>
<tr>
<td>NN</td>
<td>+ + +</td>
<td>+</td>
<td>+ + +</td>
<td>_</td>
<td>0-2wk</td>
<td>↓ liver</td>
<td>Ferritin</td>
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<tr>
<td>Haemochromatosis</td>
<td></td>
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<td>Buccal bx?</td>
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<tr>
<td>Wilson’s Disease</td>
<td>+</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td>&gt;5yrs</td>
<td>↑ retic</td>
<td>Copper</td>
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<tr>
<td>Lysosomal Disorders</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>_</td>
<td>0-4wk</td>
<td>ascites</td>
<td>studies</td>
</tr>
<tr>
<td>Bile acid defects</td>
<td>++</td>
<td>±</td>
<td>+</td>
<td>_</td>
<td>&gt;2mo</td>
<td>Ricket</td>
<td>Marrow</td>
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<td></td>
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<td>Steator</td>
<td>WBC enzyme</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>↓ GGT</td>
<td>bileacid study</td>
</tr>
</tbody>
</table>
Metabolic Liver Disease

Neonatal Ascites (2%)

- Significant hepatosplenomegaly
  - Wolman’s, Gaucher’s, MPS VII, Gangliosidosis, Sialidosis II
  - HLH (with coagulopathy)

- Cirrhosis (splenomegaly, portal hypertension)
  - Alpha-1-antitrypsin deficiency

- Small liver (coagulopathy)
  - Neonatal hemachromatosis
Metabolic liver disease presenting as acidosis

- **Blood pH**
  - **Acidosis & ketosis**
    - **L/P ratio**
      - Normal (<20)
        - Pyruvate DH deficiency
      - Increased (>20)
        - Mitochondrial disorders
    - **Organic acidaemias**
      - Prop.acidaemia
      - MM acidaemia
      - IV acidaemia
      - Glu.acidaemia
    - **Fatty ac ox defects**
      - MCAD
      - LCAD
      - LCHAD
      - GAII
  - **Normal or alkalosis**
    - **Urea cycle defects**

**Muscle Bx**
**Liver Bx**

- Resp chain enzyme
- Mitoch DNA
MANAGEMENT OPTIONS;
NON-TRANSPLANT

Dietary restriction
- galactosemia, fructosemia

Enzyme inhibition
- tyrosinemia type I (NTBC)

Enzyme induction
- Crigler-Najjar type II (phenobarbitone)

Replacement of the deficient metabolite
- inborn errors of bile acids (cholic acid)

Removal of the toxin
- Wilson disease (penicillamine, trientine, zinc)
Metabolic liver disease

MANAGEMENT OPTIONS;  
TRANSPLANT

Cirrhotic liver disease
- Orthotopic whole liver replacement

Non-cirrhotic single enzyme metabolic disease
- Auxiliary liver transplantation (Rela et al. Arch Surg 1999)
COMBINED TRANSPLANT OPTIONS

Liver + kidney

- Primary hyperoxaluria
  (Watts et al, QJM 1985)
- Methyl Malonic Acidemia

Liver + /islet cells/Pancreas

- Cystic Fibrosis
What would be an ideal treatment for Metabolic defects?

- Dietary/ Medical therapy
- Failing which – Liver transplantation

But our long-term aim is - Gene Therapy

However if the target organ is replaced the option will not be there!
Indications In Children
KCH data

- Extrahepatic Biliary Atresia 43%
- *Metabolic disorders* 23%
- Acute liver failure 23%
- Viral 1%
- Others (inc tumours) 10%
A1 antitrypsin deficiency (PIZZ), Wilson's disease, Crigler-Najjar syndrome Type I, Neonatal haemochromatosis, Glycogen storage disease type I IV, Metabolic / mitochondrial disorder, Tyrosinaemia, CD 40 ligand deficiency, Delta 3-oxosteroid 5 beta reductase deficiency, Fatty acid oxidation defects, Inborn error of fatty acid oxidation, Primary hyperoxaluria, Propionic acidaemia,
What is the downside of whole liver replacement?

Not futuristic !!
Auxiliary Liver

Donor

Recipient
Auxiliary liver transplantation for non-cirrhotic metabolic diseases
Liver Based Metabolic Disorders

Cirrhosis

- Alpha-1-antitrypsin deficiency
- Wilson’s disease
- Progressive familial intrahepatic cholestasis (PFIC)
- Perinatal haemochromatosis
- Tyrosinemia type I
- Glycogen storage disease type I, III and IV
- Fatty acid oxidation defects
- Cystic fibrosis
- Mitochondrial cytopathies

Non cirrhotic

- Propionic acidemia
- Methyl-malonic acidemia
- Primary hyperoxaluria
- Homozygous hypercholesterolemia
- Crigler-Najjar syndrome type I
- ? Urea cycle disorders
- Haemophilia (factor 7)
- Others (PKU, MSUD)
Auxiliary Partial Orthotopic Liver Transplantation for Crigler-Najjar Syndrome Type I

Mohamed Rela, FRCS, Paolo Muiesan, MD, Hector Vilca-Melendez, MD, Anil Dhawan, MD, Alaster Baker, MRCP, Giorgina Mieli-Vergani, PhD, and Nigel David Heaton, FRCS

Figure 2. Postoperative total serum bilirubin levels after auxiliary partial orthotopic liver transplantation.
Auxiliary liver tx for Propionic acidemia
10 yr follow up (Puppi, Dhawan et al AJT 2007)
Auxiliary Tx Follow up (7yrs)

- Hepatocyte Tx followed by Auxiliary Tx for OTC a novel treatment
  - Normal Ammonia
  - No dietary restrictions

  Dhawan A et al. AJT 2008
Timing of Transplantation

- Emergency OLT (ALF as presentation)

  - Wilson’s Disease
  - Neonatal Haemochromatosis
  - Urea cycle defects

  Disease specific criteria

  - Wilson’s Index
  - Risk of neurological damage
  - (encephalopathy)
Hepatocyte Transplantation

Donor

Recipient

Repopulation
Liver Plate

Transplanted Hepatocytes

Endothelial activation

Matrix proteases

Reactive O$_2$ sp.

O$_2$ + O$_2$ + OH$^-$

Xanthine oxidase

H$_2$O$_2$

Adhesion molecules and signals

VEGF/VPF, Growth factors

Perfusion

Kupffer cell/stimulation

Apoptosis

O$_2$

NADPH Oxidase

INN, ILI, INF

Liver Plate

Liver Plate

Liver Plate
Hepatocyte Tx in Children with Genetic Metabolic Liver Disease

- Crigler-Najjar Syndrome Type I (2)

*Bile samples*

- Bilirubin glucuronides detected (mainly monoglucuronides)
- Low activity of bilirubin UDP-glucuronosyltransferase
Hepatocyte Transplantation for Inherited Factor VII Deficiency

Anil Dhawan, Ragai R. Mitry, Robin D. Hughes, Sharon Lehec, Claire Terry, Sanjay Bansal, Rupen Arya, Jim J. Wade, Anita Verma, Nigel D. Heaton, Mohamed Rela, Giorgina Mieli-Vergani

<table>
<thead>
<tr>
<th>TABLE 1. Details of hepatocyte infusions in children with FVII deficiency</th>
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<tbody>
<tr>
<td>Patient 1</td>
</tr>
<tr>
<td>Age at time of first infusion</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>No. of infusions</td>
</tr>
<tr>
<td>Total no. of cells</td>
</tr>
<tr>
<td>Cell viability (%)</td>
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<tr>
<td>Portal pressure (mm Hg)</td>
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<td></td>
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<tr>
<td>Dose of rFVIIa (µg/kg/day)</td>
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</table>

*Median (range).*

cryo, cryopreserved hepatocytes; FVII, factor VII; rFVIIa, recombinant factor VIIa.

**FIGURE 1.** Daily dose of recombinant factor VIIa (rF-VIIa) in patients receiving hepatocyte transplantation. Patient 1 (open circle) and patient 2 (filled circle). OLT, orthotopic liver transplantation; TP, transplantation.
Conclusions

- Diagnosis requires high degree of suspicion
- Investigations are usually demanding and long turn around time
- Clinical suspicion should start the management to avoid neurological damage
- Liver transplantation an effective and safe mode of treatment for specific liver based metabolic disorders
- Auxiliary Liver Transplant could be a modern approach for non cirrhotic disorders while we await cell therapy or gene therapy to establish
You may say we donot have investigations
I will say....
Strive for excellence
You could bring change ..... 
If you wont, who will ?