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Tarikh : 9 Mei 2022

**SENARAI EDARAN**

YBhg. Datuk/Dato' Indera/Datin Paduka/Dato'/Datin/Tuan/Puan,

**SURAT PEKELILING KETUA PENGARAH KESIHATAN MALAYSIA BIL. 10/2022**

**PROTOKOL PENGURUSAN KES HEPATITIS AKUT TIDAK DIKETAHUI PENYEBABNYA (*ACUTE HEPATITIS OF UNKNOWN AETIOLOGY*) DALAM KALANGAN KANAK-KANAK**

## 1. TUJUAN

1.1 Surat Pekeliling ini bertujuan untuk memaklumkan protokol pengurusan kes Hepatitis Akut Tidak Diketahui Penyebabnya (*Acute Hepatitis Of Unknown Aetiology*) dalam kalangan kanak-kanak.

## 2. LATAR BELAKANG

2.1 Pada 23 April 2022, Pertubuhan Kesihatan Sedunia (WHO) melalui WHO *Event Information Site* (EIS) telah melaporkan kejadian Hepatitis Akut Tidak Diketahui Penyebabnya (*Acute Hepatitis of Unknown Aetiology*) yang berlaku dalam kalangan kanak-kanak berumur antara satu (1) bulan hingga 16 tahun.

2.2 Sehingga 21 April 2022, WHO telah menerima pelaporan sebanyak 169 kes melibatkan 12 buah negara. Kes tertinggi sebanyak 114 dilaporkan di United Kingdom. Negara lain yang turut melaporkan kes adalah Sepanyol, Israel, Amerika Syarikat, Denmark, Ireland, Itali, Belanda,

Perancis, Norway, Belgium dan Romania. Setakat ini hanya satu (1) kematian telah dilaporkan.

2.3 Kejadian hepatitis akut yang dilaporkan ini dikategorikan sebagai Hepatitis Akut yang Tidak Diketahui Penyebabnya kerana virus hepatitis A, B, C, D atau E yang merupakan penyebab lazim hepatitis tidak dikesan melalui ujian makmal. Pada masa yang sama, laporan daripada WHO menunjukkan sebanyak 74 kes dikesan positif *Adenovirus* dan 20 kes dikesan positif SARS-CoV-2. Walau bagaimanapun penyebab hepatitis akut ini belum dapat ditentusahkan dan masih dalam siasatan.

2.4 Sehubungan dengan itu, Kementerian Kesihatan (KKM) perlu mempertingkatkan survelan bagi hepatitis akut di semua klinik kesihatan dan hospital dengan menggunakan definisi kes yang telah dipersetujui oleh pakar-pakar perubatan (kanak-kanak, penyakit berjangkit, gastroentrologi, patologi dan kesihatan awam).

## 3. PROTOKOL PENGURUSAN KES HEPATITIS AKUT TIDAK DIKETAHUI PENYEBABNYA (*ACUTE HEPATITIS OF UNKNOWN AETIOLOGY*) DALAM KALANGAN KANAK-KANAK

3.1 Semua pengamal perubatan di klinik kesihatan kerajaan dan swasta dikehendaki merujuk kanak-kanak berumur satu (1) bulan hingga kurang dari 18 tahun yang menunjukkan gejala jaundis dan gejala lain hepatitis akut seperti hilang selera makan, loya, muntah, kelesuan, ketidakselesaan abdomen atau air kencing berwarna gelap ke hospital untuk pengurusan kes selanjutnya. Maklumat kes disyaki hepatitis akut yang dirujuk ke hospital perlu dihantar kepada Pejabat Kesihatan Daerah (PKD) menggunakan format di **Lampiran 1**.

3.2 PKD pula hendaklah menghantar maklumat tersebut kepada Pusat Kesiapsiagaan dan Tindak Cepat Krisis (CPRC) Kebangsaan, KKM secara mingguan pada setiap hari Isnin minggu berikutnya. Maklumat ini akan digunakan bagi menyemak dan mengemaskini definisi kes hepatitis akut dalam negara.

3.3 Pengamal perubatan di hospital kerajaan dan swasta pula dikehendaki melaporkan kes Hepatitis Akut Tidak Diketahui Penyebabnya (*Acute Hepatitis Of Unknown Aetiology*) yang memenuhi kriteria kes *probable* kepada Pusat Kesiapsiagaan dan Tindak Cepat Krisis (CPRC) Jabatan Kesihatan Negeri (JKN) dan CPRC Kebangsaan KKM dalam tempoh 24 jam menggunakan Borang Notifikasi seperti di **Lampiran 2**. Notifikasi kepada KKM dibuat melalui email: cprckkm@moh.gov.my. Notifikasi ini perlu bagi KKM memantau tren kejadian hepatitis akut dalam negara serta keperluan melaporkan kes kepada Pertubuhan Kesihatan Sedunia (WHO), seperti yang disarankan.

3.3 CPRC JKN akan memaklumkan PKD mengenai kes hepatitis akut yang dinotifikasi ini untuk siasatan lanjut. Borang siasatan akan diemelkan oleh CPRC Kebangsaan kepada Pegawai Epidemiologi Negeri (Penyakit Berjangkit) untuk dikongsikan dengan Pegawai Kesihatan Daerah.

3.4 Protokol Pengurusan Kes Hepatitis Akut Tidak Diketahui Penyebabnya adalah seperti di **Lampiran 3.**

## 4. TARIKH BERKUATKUASA

Surat Pekeliling ini berkuatkuasa mulai dari tarikh surat ini.

## 5. PERTANYAAN

Sekiranya terdapat sebarang pertanyaan, sila kemukakan kepada :-

Pengarah Perkembangan Perubatan
Aras 7, Blok E1, Parcel E, Kompleks Kerajaan Persekutuan
62590 Putrajaya
No. Telefon : 03 – 8883 1047

atau

Pengarah Kawalan Penyakit
Aras 3, Blok E10, Parcel E, Kompleks Kerajaan Persekutuan
62590 Putrajaya
No. Telefon : 03 – 8883 4419 / 03 – 8883 4118

**7. PENUTUP**

YBhg. Datuk / Dato' Indera / Datin Paduka / Dato' / Datin / Tuan dan Puan adalah bertanggungjawab untuk memastikan pekeliling ini dihebahkan dan dan dipatuhi.

Sekian, terima kasih.

**"WAWASAN KEMAKMURAN BERSAMA 2030"**

**"BERKHIDMAT UNTUK NEGARA"**

*Saya yang menjalankan amanah,*

**(TAN SRI DATO' SERI DR. NOOR HISHAM BIN ABDULLAH)**

**SENARAI EDARAN**

Timbalan Ketua Pengarah Kesihatan (Perubatan)
Kementerian Kesihatan Malaysia

Timbalan Ketua Pengarah Kesihatan (Kesihatan Awam)
Kementerian Kesihatan Malaysia

Timbalan Ketua Pengarah Kesihatan (Penyelidikan & Sokongan Teknikal)
Kementerian Kesihatan Malaysia

Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia

Pengarah Perkembangan Perubatan
Kementerian Kesihatan Malaysia

Pengarah Kawalan Penyakit
Kementerian Kesihatan Malaysia

Pengarah Pembangunan Kesihatan Keluarga
Kementerian Kesihatan Malaysia

Pengarah Amalan Perubatan
Kementerian Kesihatan Malaysia

Pengarah Perkembangan Kesihatan Awam
Kementerian Kesihatan Malaysia

Pengarah Pendidikan Kesihatan
Kementerian Kesihatan Malaysia

Pengarah
Hospital Kuala Lumpur

Pengarah Kesihatan Negeri Perlis
Jabatan Kesihatan Negeri Perlis

Pengarah Kesihatan Negeri Kedah
Jabatan Kesihatan Negeri Kedah

Pengarah Kesihatan Negeri Pulau Pinang
Jabatan Kesihatan Negeri Pulau Pinang

Pengarah Kesihatan Negeri Perak
Jabatan Kesihatan Negeri Perak

Pengarah Kesihatan Negeri Selangor
Jabatan Kesihatan Negeri Selangor

Pengarah Kesihatan WP Kuala Lumpur & Putrajaya
Jabatan Kesihatan WP Kuala Lumpur & Putrajaya

Pengarah Kesihatan Negeri Sembilan
Jabatan Kesihatan Negeri Sembilan

Pengarah Kesihatan Negeri Melaka
Jabatan Kesihatan Negeri Melaka

Pengarah Kesihatan Negeri Johor
Jabatan Kesihatan Negeri Johor

Pengarah Kesihatan Negeri Pahang
Jabatan Kesihatan Negeri Pahang

Pengarah Kesihatan Negeri Terengganu
Jabatan Kesihatan Negeri Terengganu

Pengarah Kesihatan Negeri Kelantan
Jabatan Kesihatan Negeri Kelantan

Pengarah Kesihatan Negeri Sarawak
Jabatan Kesihatan Negeri Sarawak

Pengarah Kesihatan Negeri Sabah
Jabatan Kesihatan Negeri Sabah

Pengarah Kesihatan WP Labuan
Jabatan Kesihatan WP Labuan

Pengarah
Institut Penyelidikan Klinikal

Pengarah
Institut Penyelidikan Perubatan

Pengarah
Makmal Kesihatan Awam Kebangsaan
Sungai Buloh

Ketua Pengarah
Kementerian Pengajian Tinggi
Putrajaya

Ketua Pengarah
Perkhidmatan Kesihatan Angkatan Tentera Malaysia
Kementerian Pertahanan Malaysia

Pengarah
Pusat Perubatan Universiti Malaya (PPUM)
Kuala Lumpur

Pengarah
Pusat perubatan Universiti Kebangsaan Malaysia (PPUKM)
Kuala Lumpur

Pengarah
Kampus Kesihatan Universiti Sains Malaysia
Kubang Kerian, Kelantan

Pengarah
Hospital Pengajar Universiti Putra Malaysia (UPNM)

Pengarah
Hospital UiTM Sg Buloh

Presiden
Persatuan Perubatan Malaysia (MMA)

Presiden
Persatuan Hospital Swasta Malaysia (APHM)

**Lampiran 1**

**RETEN MINGGUAN**
**KES DISYAKI "HEPATITIS AKUT YANG TIDAK DIKETAHUI PENYEBABNYA" YANG DIRUJUK KE HOSPITAL**

**Tarikh: _____**

| BIL. | TARIKH | NAMA | NO. KAD PENGENALAN | JANTINA (L / P) | ALAMAT | GEJALA |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

**Nama pengamal perubatan: .....**

**Cop klinik: .....**

**Lampiran 2**

**NOTIFICATION FORM**
**FOR ACUTE HEPATITIS OF UNKNOWN AETIOLOGY**

**Disease Control Division**
**Ministry Of Health Malaysia**

| | | | |
|---|---|---|---|
| **1.Reporting Centre** | **Name of Hospital / Clinic:** | | **State:** |
| Phone: | Fax: | E-mail: | |
| **Information of Patient** | **Name:** | Age:___yr ___mth | **Gender:** ☐Male ☐Female |
| **Address:** | | Phone (Home): | RN No: |
| **Nationality:** ☐Malaysian ☐Non Malaysian | ***Ethnicity:*** ☐Malay ☐Chinese ☐Indian ☐ *Other, specify:* | | IC No: |
| | Country of Origin: | | Passport No: |
| **Student** : | ☐ Yes. If yes, please state name of institution: ..... ☐ No | | **Date of symptom onset** *[dd/mm/yy] :* |
| **3. Signs and Symptoms** | ☐ Jaundice | | |
| | Other symptoms of acute hepatitis: ☐ Vomiting ☐ Malaise ☐ Right upper quadrant pain ☐ Dark coloured urine ☐ Nausea ☐ Anorexia ☐ Extreme fatigue ☐ *Other symptoms, specify : ..... | | |
| **4. Patient ever been positive COVID-19?** | **Past Infection** ☐ Yes, date positive: _____ ☐ No<br>**Current Infection** ☐ Yes, date positive: _____ ☐ No | | |
| **5. Has the patient received COVID-19 vaccination?** | ☐ Yes. If yes, Type of vaccine: Comirnaty / Sinovac / others: ..... How many doses: 1 dose / 2 doses / 3 doses.<br>☐ No | | |
| **6. Is there any alternative diagnosis that can fully explain patient's illness?** | ☐Yes, please specify: ..... ☐ No | | |
| **7. Clinical status at time of report** | Was patient hospitalised? ☐ Yes, date: _____ ☐ No ☐ Brought in dead (BID) | Ward: ☐ Isolation ward ☐ General ward ☐ ICU | Progress: ☐On treatment, specify: _____ ☐ Died *Date :*_____ |
| *If patient died:* Was past mortem performed? | ☐ Yes ☐No ☐ Pending | | |
| **8. Exposure History** | Has patient in close contact with any jaundice case? ☐ *Yes* ☐*No* | | |
| | ***If yes, please specify:*** | | |
| **9. Similar illness** | Anybody in the neighbourhood having similar illness? ☐**Yes** ☐ **No** | | |
| **10. Diagnostic Evaluation** | Date taken | Result | |
| **AST/ALT value** | | | |
| **Virology** | | Hepatitis A ☐ Positive ☐ Negative ☐ Pending<br>Hepatitis B ☐ Positive ☐ Negative ☐ Pending<br>Hepatitis C ☐ Positive ☐ Negative ☐ Pending<br>Hepatitis D ☐ Positive ☐ Negative ☐ Pending<br>Hepatitis E ☐ Positive ☐ Negative ☐ Pending<br>Adenovirus ☐ Positive ☐ Negative ☐ Pending<br>Other tests, please specify: _____ | |
| **11. Working diagnosis:** *(please state)* | | | |
| **12. Reporting Officer:** | | | Signature: |
| Designation: | **Date:** | | H/phone No: |
| **For State Health Department use only** | | | |
| **13. Name of receiving officer:** | | | Signature: |
| Designation: | Date: | | H/Phone No: |
| **14. Date of notification to District Health Office:** | | | |
| **For Disease Control Division use only** | | | |
| **COMMENTS:** | | | |
| **Date of notification to State Health Department:** | | | |

# PROTOKOL PENGURUSAN KES HEPATITIS AKUT TIDAK DIKETAHUI PENYEBABNYA (*ACUTE HEPATITIS OF UNKNOWN AETIOLOGY*) DALAM KALANGAN KANAK-KANAK

**Acute Hepatitis of Unknown Aetiology in Children and Adolescents**

- **Case management and investigations**

## A. OBJECTIVE

This document provides a guide for assessment and management of children suspected or confirmed case of Acute Hepatitis of Unknown Aetiology.

## B. CASE DEFINITION

### (i) SUSPECTED CASE:

Children aged 1 month to less than 18 years old presenting with jaundice and other evidence of acute hepatitis such as:-

- dark coloured urine
- anorexia
- malaise
- extreme fatigue
- nausea
- vomiting
- right upper quadrant pain

### (ii) PROBABLE CASE:

Children aged 1 month to less than 18 years old presenting with jaundice and other evidence of acute hepatitis such as:-

- dark coloured urine
- anorexia
- malaise
- extreme fatigue
- nausea
- vomiting
- right upper quadrant pain

AND

• Increased urine urobilinogen with serum transaminase >500 IU/L (AST or ALT)

AND

• Non Hep A, B, C, D and E

*Note: Cases with other explanations for their clinical presentation are discarded*

## C. HEALTH EDUCATION**

### (i) PREVENTIVE MEASURES FOR PUBLIC

- Wash hands often with soap and water for at least 20 seconds.
- Avoid touching eyes, nose, or mouth with unwashed hands.
- Avoid close contact with people who are sick.

### (ii) PREVENTIVE MEASURES FOR PATIENTS

- Stay home when you are sick.
- Cough and sneeze into a tissue or upper shirt sleeve, not on hands.
- Avoid sharing cups and eating utensils with others.
- Refrain from kissing others.
- Wash hands often with soap and water for at least 20 seconds, especially after using the bathroom.

## D. ASSESSMENT

- All patients suspected or confirmed to have **acute hepatitis** should be referred to nearby hospitals with paediatrician / paediatric gastroenterologist / hepatologist / physician for further assessment.
- Patient meeting acute liver failure criteria (refer Paediatric Acute Liver Failure Criteria / Adult Acute Liver Failure Criteria) should be referred to gastroenterologist / hepatologist / liver transplant centre.

**Paediatric Acute Liver Failure (ALF) criteria[1]**

(i) Acute onset of liver disease without evidence of chronic liver disease

(ii) Biochemical evidence of severe liver injury

- Coagulopathy not corrected by vitamin K
  - Prothrombin time (PT) ≥15 s or INR ≥1.5 with evidence of hepatic encephalopathy (HE) or
  - PT ≥20 s or INR >2 with or without encephalopathy

**Adult Acute Liver Failure (ALF) criteria[2]**

Severe acute liver injury defines a syndrome characterised by markers of liver damage (elevated serum transaminases) and impaired liver function (jaundice and INR >1.5) which usually precedes clinical encephalopathy. (Ref EASL)

***Acute liver failure is defined as any degree of encephalopathy and coagulopathy (INR > 1.5) due to an illness of less than 24 weeks duration.***

**Flow chart for Management Of Acute Hepatitis Of Unknown Aetiology In Primary Care : See Appendix 1**

**Aetiologies for acute severe hepatitis**

The aetiologies of the acute hepatitis in children varies according to age group. **See Appendix 2.**

**Assessment should begin with comprehensive clinical history and physical examination.**

**(i) HISTORY**

- Symptoms of acute hepatitis
  - fatigue, malaise, nausea, and abdominal pain / discomfort
  - jaundice, dark urine, pale or light-coloured stool

- Other associated symptoms (varies based on age and aetiology)
  - fever
  - anorexia, vomiting, diarrhoea, bloody stool
  - headache
  - conjunctivitis

- irritability / confusion / altered mentation
- rashes
- respiratory symptoms, sore throat

- Drug history e.g. paracetamol (could be unintentional overdose), NSAIDs (Aspirin - Reye's syndrome), antibiotics, dietary supplements and herbal medicine; other toxins ingestion / recent food intake e.g. mushroom (Amanita Phalloides, Amanita verna), shellfish.

- Travel history (e.g. tropical diseases, HAV and Hepatitis E infection), sick contact history, family history (autoimmune conditions, Wilson disease, inborn error of metabolism, consanguinity).

- History of high risk activities e.g. illicit drug use, alcohol consumption, sexual history, paracetamol intentional ingestion (for adolescent group of patients).

- Past medical history e.g. history of blood transfusion, a recent history of dehydration (acute Budd Chiari syndrome), recent events which could potentially predispose to hypotension/ vascular/ hypoxic insults to the liver (ischemic hepatopathy), recurrent infections (primary immunodeficiencies).

- History of previous COVID-19 infection.

- Vaccination history : COVID-19 vaccination (vaccine brands, completeness, last dose etc).

**(ii) PHYSICAL EXAMINATION**

- Physical examination may be unremarkable in the early stages of ALF.
- General examination: jaundice, pallor, bruises, asterixis, hydration.
- Blood pressure, pulse rate, pupillary sizes and reactions for Cushing reflex.
- Initial, and serial neurological examinations should be performed to assess mental (e.g., attentiveness, confusion, orientation) and neurological signs of hepatic encephalopathy (e.g., brisk reflexes, hypertonia, sustained clonus, Babinski sign)

- Hepatic encephalopathy grading **(see Appendix 3)**
- Abdominal examination – Liver (size, consistency, tenderness), spleen (enlargement), ascites, abdominal tenderness (cholecystitis, ascending cholangitis), abdominal mass.
- Lymph nodes assessment (malignancy, infection).
- Cardiovascular assessment – right heart failure (hepatic congestion, Budd Chiari).
- Signs suggestive of an underlying chronic liver disease :-
  - growth failure, dysmorphism
  - portal hypertension (abdominal varices, hepatosplenomegaly, ascites)
  - digital clubbing, rachitic rosary
  - skin xanthomas, spider angiomas palmar erythema, caput medusae, gynaecomastia
  - eye examination: signs of metabolic liver disease eg: cataracts, Kayser- Fleischer rings, cherry red spots etc.

**Red flags of worsening liver disease: Salient features**

- Persistent / progressive jaundice with clinically impalpable liver / rapid reduction of liver size, with progressive decline in serum aminotransferase levels.
- Declining conjugated bilirubin level.
- Progressive encephalopathy (needs frequent review).
- Increasing lethargy $\pm$ hallucinations.
- Symptoms like mild changes in behaviours may be subtle and not detectable by clinical assessment but are apparent to family members :-
  - Personality changes: e.g. irritable / apathetic (young children), aggression, irritability, euphoria, apathy (older).
  - Intellectual deterioration, insomnia, sleep inversion.
- Bruising, petechiae or bleeding from deranged clotting unresponsive to intravenous / subcutaneous vitamin K.
- Persistent hypoglycaemia (which aggravates encephalopathy).
- Progressive hyperammonaemia.

- Signs of raised intracranial pressure (sluggish dilated pupils, bradycardia, hypertension or papilloedema).

## D. INVESTIGATIONS

### (i) Initial clinical testing:

- Liver function: PT / INR / Bilirubin (total and fractionated) / Total Protein and Albumin / Glucose / Ammonia
- Multisystem assessment: RP /Ca / Mg /PO4 /FBC /Amylase / Blood Gas / Lactate
- Liver injury: ALT / AST / GGT / Ferritin

** To monitor regularly (at least daily) and watch out for worsening liver disease indicated by persistent jaundice, worsening coagulopathy with impalpable liver or a liver of reducing size, with progressive decline in serum aminotransferase levels

### (ii) Investigations of aetiology:

Every possible cause leading to acute hepatitis including infections, toxins or autoimmune and metabolic causes must be investigated.

**1. Infection :**

- IgM anti-HAV
- HBsAg, IgM anti-HBcore (if HBsAg was negative)
- Anti-HCV
- IgM anti-HDV / PCR (if HepBsAg positive)
- IgM anti-HEV / PCR
- Parvovirus IgM
- IgM anti EBV / PCR
- Herpes virus IgM (HSV 1&2, HHV6, HHV7)
- IgM anti-CMV / PCR
- Adenovirus PCR
- Dengue serology
- Leptospiral serology (if clinically indicated)
- Blood culture/Urine culture/Stool culture (bacteria)
- Respiratory panel multiplex PCR (Influenza, Parainfluenza, RSV, Metapneumovirus) (if there is respiratory symptom)

- SARS-COV2 PCR +/- , SARS-COV2 Antibody
- Stool for multiplex PCR-GI Pathogens including Rotavirus / Norovirus / Adenovirus / Enterovirus / Astrovirus / Sapovirus (if there is gastrointestinal symptoms)

**2. Autoimmune panel :**

- Serum immunoglobulin IgG / A / M
- Anti Nuclear Antibody
- ANCA
- Liver Auto Antibodies (anti-smooth muscle antibodies, anti-liver kidney microsomal antibodies, liver antibodies)

**3. Metabolic :**

- Plasma amino acid
- Urine organic acid
- Blood spot for Acylcarnitine profile
- Serum Ceruloplasmin
- 24-urine for copper + Penicillamine Challenge

**4. Toxicology :**

- Serum Paracetamol level
- Serum Salicylate level
- Consider urine toxicology if there are suggestive symptoms

**5. Liver biopsy (to be considered including post mortem and liver explant sampling)**

- Histopathology (H&E staining, special immunohistochemical staining, dry weight liver copper) – according to clinical suspicion.
- Liver tissue culture and PCR (VTM / saline if for viral culture).

**6. Others :**

- Full blood picture
- Ferritin
- Lipid profile (including triglyceride)

In light of recent SARS-COV-2 pandemic (Covid-19) – MISC is a rare complication following SARS-COV-2 infection.

For consideration of C-reactive protein, ESR, D-dimer, Ferritin, fibrinogen, Procalcitonin, Creatine kinase (+/- cardiac markers – Troponin, BNP or N-terminal pro-BNP), ECG (repolarization changes with abnormal ST- or T wave segments).

**Figure 1 illustrates the diagnostic approach for laboratory investigation of acute hepatitis of unknown aetiology and Table 1 shows the list of laboratories conducting the tests.**

## Figure 1 : The Laboratory Diagnostic Approach For Acute Hepatitis of Unknown Aetiology

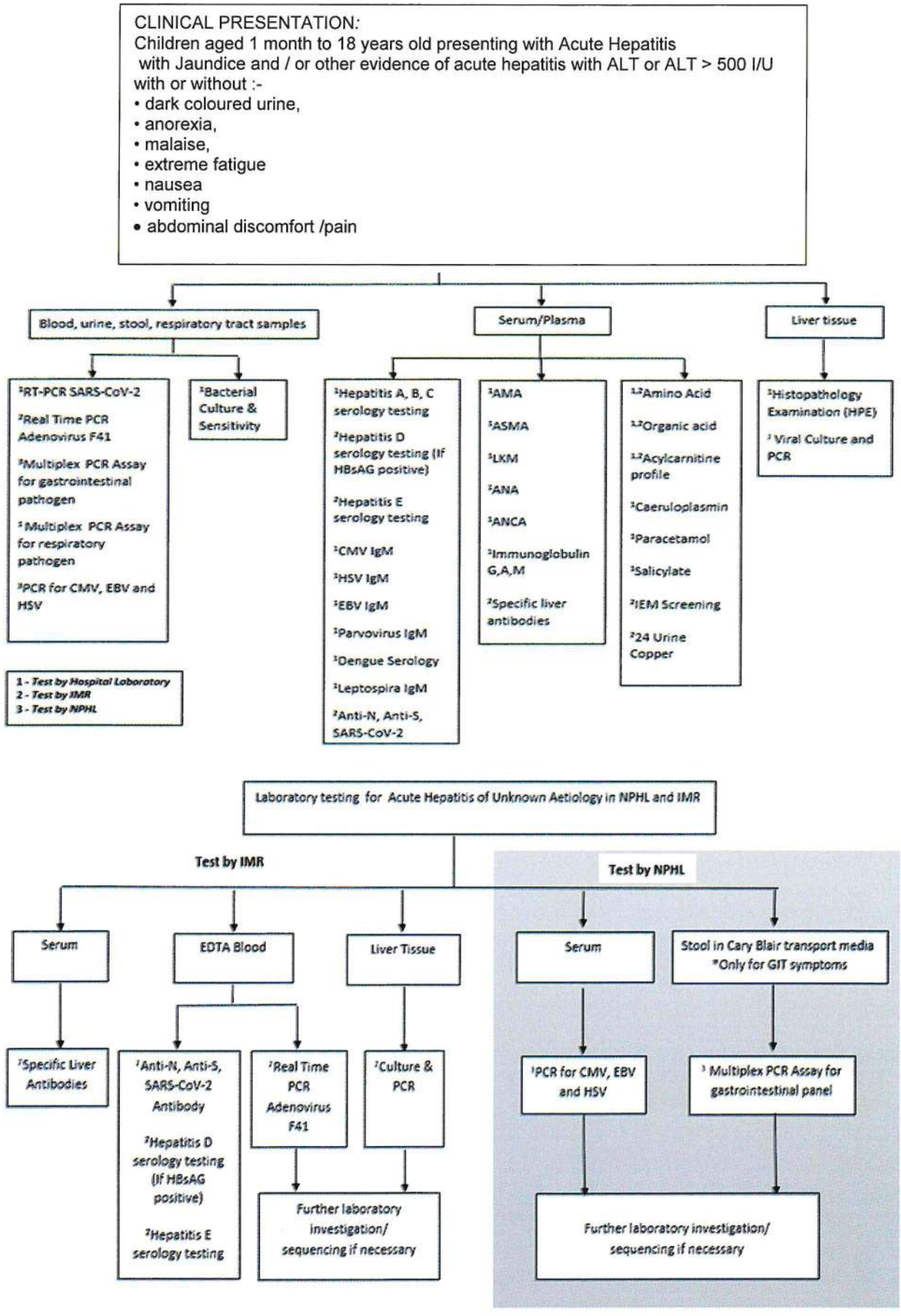


**Table 1 : Lists Of Tests For Suspected Case Of Hepatitis Of Unknown Aetiology**

**1. BACTERIOLOGY TESTS**

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | Bacterial Culture & Sensitivity | Blood, Respiratory, Stool, Tissue, Pus, Swab, Urine | State Hospital / Major Specialist Hospitals | Send as soon as possible to the laboratory |

**2. VIROLOGY / SEROLOGY TESTS**

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | Hepatitis A IgM | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |
| 2. | Hepatitis B surface Antigen (HBsAg) | Serum (Plain tube) | State Hospitals / Major Specialist Hospitals | 3-5 mls of blood |
| 3. | Hepatitis B Core IgM | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |
| 4. | Hepatitis C Antibody | Serum (Plain tube) | State Hospitals / Major Specialist Hospitals | 3-5 mls of blood |
| 5. | Hepatitis D IgM (only when HBsAg is positive) | Serum (Plain tube) | IMR / NIH | 3-5 mls of blood |
| 6. | Hepatitis E IgM | Serum (Plain tube) | IMR / NIH | 3-5 mls of blood |
| 7. | CMV IgM | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |

| | | | | |
|---|---|---|---|---|
| 8. | HSV IgM | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |
| 9. | EBV IgM | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |
| 10. | Parvovirus IgM | Serum (Plain tube) | Hospital Sungai Buloh | 3-5 mls of blood |
| 11. | Dengue Serology (NS1 / IgM / IgG) | Serum (Plain tube) | State Hospitals / Major Specialist Hospitals | 3-5 mls of blood |
| 12. | Leptospira IgM | Serum (Plain tube) | State Hospitals / Major Specialist Hospitals | 3-5 mls of blood |
| 13. | SARS-COV2 Antibody | Plasma (EDTA tube) | IMR / NIH | 3-5 mls of blood |

**3. MOLECULAR TESTS**

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | SARS-COV2 PCR | NPS & OPS Swab in VTM | State Hospitals | Transport in ice and triple packaging |
| 2. | Adenovirus F41 PCR | Plasma (EDTA tube), Liver biopsy (sterile container in saline, not in paraffin) | IMR / NIH | Transport in ice and triple packaging |
| 3. | CMV PCR | Serum / Plasma | MKAK Sg Buloh | Transport in ice and triple packaging |

| | | | | |
|---|---|---|---|---|
| 4. | HSV PCR | Serum / Plasma | MKAK Sg Buloh | Transport in ice and triple packaging |
| 5. | EBV PCR | Serum / Plasma | MKAK Sg Buloh | Transport in ice and triple packaging |
| 6. | PCR for GIT Panel | Stool in Cary Blair | MKAK Sg Buloh | Transport in ice and triple packaging |
| 7. | PCR for Respiratory Pathogens | NPS in UTM / VTM | State Hospitals | Transport in ice and triple packaging |

**4. IMMUNOLOGY TESTS**

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | IgA, IgM and IgG | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |
| 2. | Anti-Nuclear Antibody (ANA) | Serum (Plain tube) | State Hospitals | 3-5 mls of blood |
| 3. | Anti-Mitochondrial Antibody (AMA) | Serum (Plain tube) | Regional Centres | 3-5 mls of blood |
| 4. | Anti-Smooth Muscle Antibody (ASMA) | Serum (Plain tube) | Regional Centres | 3-5 mls of blood |
| 5. | Liver-Kidney Microsomal (LKM) Antiibody | Serum (Plain tube) | Regional Centres | 3-5 mls of blood |
| 6. | Specific Liver Antibodies (SLA) Panel - Anti-AMA-M2, M2 3E/BPO, Sp | Serum (Plain tube) | IMR / NIH | 3-5 mls of blood |

| | | | | |
|---|---|---|---|---|
| | 100, PML, gp210, LKM1, LC-1, SLA/LP, Ro-52 | | | |

**5. METABOLIC TESTS**

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | Amino acid | Plasma(Lithium Heparin) | IMR & Hospital Tunku Azizah | Spin and separate plasma |
| 2. | Organic acid | Random Urine | IMR & Hospital Tunku Azizah | Transport in Ice |
| 3. | Acylcarnitine profile | Dried Blood Spot(DBS) | IMR & Hospital Tunku Azizah | 3 circle of dried blood spot using Whatmann 903 Filter paper |
| 4. | Ceruloplasmin | Serum (Plain tube) | Hospital Kuala Lumpur / Hospital Selayang | Spin and separate serum |
| 5. | 24-hr Urine Coppe | Urine (24 hour) | **NIH** | 24 hour urine container without preservative |

**6. TOXICOLOGY TESTS**

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | Paracetamol | Serum (Plain tube without gel) | State Hospitals / Major Specialist Hospitals | Spin and separate serum |

| | | | | |
|---|---|---|---|---|
| 2. | Salicylate level | Serum (Plain tube without gel) | State Hospitals / Major Specialist Hospitals | Spin and separate serum |

## 7. HISTOPATHOLOGY TESTS

| No. | NAME OF TESTS | SAMPLE TYPE | TESTING FACILITY | SAMPLE REQUIREMENT |
|---|---|---|---|---|
| 1. | Tissue for Histopathological Examination (HPE) | Liver tissue from biopsy or postmortem | Hospital Selayang (Wilayah Persekutuan, Selangor, Negeri Sembilan, Melaka, Johor, Sarawak and Sabah)<br><br>Hospital Pulau Pinang (Perlis, Pulau Pinang, Kedah, Perak, Kelantan, Terengganu and Pahang) | Tissue in paraffin block |

**(iii) Imaging**

- Ultrasound abdomen (liver size, +/- doppler study of the liver vasculature - Budd Chiari syndrome)
- Chest X-Ray (mediastinal mass, lymph nodes, lung parenchyma changes, pleural effusion, cardiomegaly etc.) +/- Echocardiography (RV/LV function)

## E. MANAGEMENT

A patient suspected or confirmed to have acute severe hepatitis of unknown aetiology should receive general management strategies regardless of the aetiology. Avoid hepatotoxic, nephrotoxic and sedative medications.

The management of acute hepatitis depends on specific aetiological causes and based on constellation of clinical findings and presentations. Most of viral hepatitis (e.g. Hepatitis A infection) usually have a self-limited course with supportive / symptomatic treatment that includes IV fluids, anti-emetics (for older children and adolescents), or other symptomatic treatment. N-acetylcysteine should be started as soon as possible in suspicion of acute paracetamol ingestion (as per treatment of paracetamol protocol).

Standard precautions must be used at all times for all patients in all situations as the aetiology could be infective and transmissible.

**IF PATIENT PROGRESSES INTO ACUTE LIVER FAILURE:**

**(i) General management:**

- **Early referral to intensive care unit if patient condition worsens or progress to liver failure**
- Closely monitored in quiet darkened room with head end elevated at 30° and head in neutral position (to decrease ICP and minimise cerebral irritability).
- DO NOT sedate unless already ventilated because it may precipitate respiratory failure and death.
- Maintain oxygenation.
- Frequent neurological observations (1-4hourly).

- Give Vitamin K in case the prolonged PT is due to its deficiency. The INR is an important prognostic marker, only correct it if there are signs of bleeding or when needed for invasive procedures. If frank bleeding (Gastrointestinal tract/Oral) occurs, consider prudent use of FFP and cryoprecipitate. Platelet count should be maintained ≥ 50 x10□/dl.
- Prophylactic H2 antagonist or proton pump inhibitor or oral antacid to prevent gastric/duodenal ulceration.
- Full septic screen (excluding Lumbar Puncture), CXR. Treat sepsis aggressively.

**(ii) Fluids**

- Maintain blood glucose ≥ 4mmol/l using minimal fluid volume (Aim to maintain hydration & renal function while reducing risk of cerebral oedema).
- Maintain euvolemia, consider 90% of normal maintenance if progressed to acute liver failure.
- Maintenance fluids consist of Dextrose 10% in 0.45% or 0.90% Normal saline.
- A central vein catheterisation should be considered for high glucose concentration delivery.
- Check capillary blood sugar every 2-4 hourly (maintain ≥ 4mmol/l).
- Strict monitoring of urine output & fluid balance (catheterisation if necessary).
- Aim urine output ≥ 0.5ml/kg/hour.
- Renal dysfunction - Possible causes: volume depletion, hepatorenal syndrome, low CVP, low cardiac output. Consider early haemofiltration or dialysis.
- In the presence of persistent hypotension (decreased SVR) – might consider IV noradrenaline infusion followed by vasopressin analogues.

  Consider IV Hydrocortisone in cases suspected of adrenal insufficiency.

**(iii) Nutrition**

- Provide adequate energy intake to avoid catabolism.

- If patient progresses to hepatic encephalopathy, consider to stop oral protein. Gradually reintroduce at 0.5-1g/kg/day, then 1-2g/kg/day either enterally or parenterally.
- Normalize Na, K, Mg, Phosphate.
- Bowel decontamination: Lactulose to produce 3-4 loose stools per day (Syrup lactulose 1-2ml/kg every 4-6hourly). Consider Neomycin or Rifaximin if available.

**(iv) Medications**

- IV N• IV N-acetylcysteine (NAC) is indicated if paracetamol poisoning in paediatrics (history and high index of suspicion are very important as occasionally blood paracetamol levels are already normal by the time the patient presents to hospital with liver failure).

***To consult hepatologist if in doubt***

- *NAC did not improve 1-year survival in non-paracetamol PALF. 1-year liver transplant free survival was significantly lower with NAC, particularly among those < 2 years old. (Ref: Squires RH, Dhawan A, Alonso E, et al. Hepatology 2013 April; 57(4):1542–1549)*
- *While in a randomized control study on adult patients with non-paracetamol ALF including patients* ***aged 18 years or older****, NAC used at an early stage of HE (grade I and II hepatic encephalopathy) had been shown to improve transplant free survival. (Ref: WM Lee et al. Gastroenterology 2009 Sep;137(3):856-64, 864.e1. doi: 10.1053/j.gastro.2009.06.006)*
- *Antibiotics: Combination that provides a good cover against gram negative organisms and anaerobes e.g. cefotaxime and metronidazole if no specific infective agent suspected (e.g. Leptospira. Mycoplasma).*
- *Antiviral: Acyclovir is recommended in ALF with the possibility of HSV infection.*
- *Antifungal if clinically suspected.*

### (v) Clinical Pearls in Comatose Patient

- In the presence of sudden coma, consider intracranial bleed: request a CT brain.
- Patients with Grade 3 or 4 Encephalopathy require mechanical ventilation to maintain normal cerebral perfusion pressure. Sedation may use a combination of opioid (morphine or fentanyl) and benzodiazepines (midazolam).
- Try to avoid peak end-expiratory pressure of >8cm H2O (may increase ICP); PaCO2 should be kept within 4-4.5 kPa.(30-35mmHg).
- Raised Intracranial pressure : consider mannitol (rapid bolus 0.5g/kg as a 20% solution over 15 minutes; can be repeated if serum osmolality is < 320 mOsm/l), induction hypernatremia using hypertonic saline (Na > 145mmol/L) and mild cerebral hypothermia (32-35□C) in refractory high ICP.

### (vi) Liver Support Therapies and Liver Transplant

ALF is a rapid evolving clinical condition with no current satisfactory tools to predict outcomes.

Consider liver support therapies e.g. total plasma exchange or MARS (discuss with intensivist).

Hence early referral to liver transplant centre (Hospital Selayang, Hospital Tunku Azizah, University Malaya Medical Centre) is crucial. Transfer of patients with possible cerebral oedema and raised intracranial pressure needs review and input by colleagues in critical care with experience in the transfer of critically ill patients.

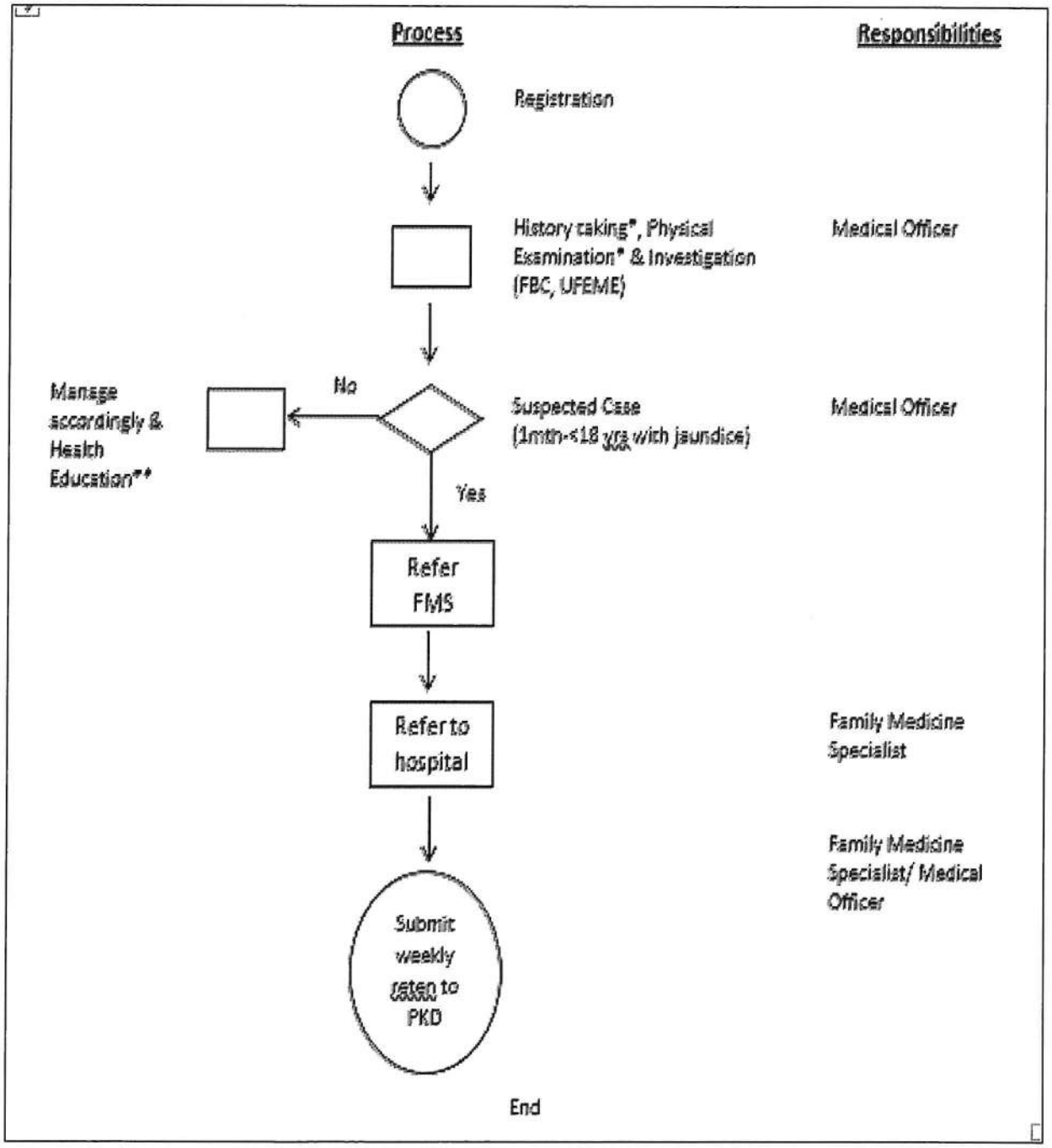
Post mortem examination should be offered to the family. A bedside post mortem trucut liver biopsy done percutaneously should be discussed with family if no consent for post mortem.

**REFERENCES:**


1. Squires JE, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. J Pediatr Gastroenterol Nutr. 2022 Jan 1;74(1):138-158.
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4. European Centre of Disease Prevention and Control: Hepatitis of Unknown Origin Reporting Protocol 2022 Version 2.0
5. Squires RH, Dhawan A, Alonso E, et al. Hepatology 2013 April; 57(4):1542–1549.)
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**Appendix 1**

## Flow chart for Management Of Acute Hepatitis Of Unknown Aetiology In Primary Care



**Appendix 2**

## Aetiology of Acute Hepatitis / Acute Liver Failure

| **1. Metabolic syndromes (10% of Paediatric Acute Liver Failure)** |
|---|
| **(i) Infants** |
| Hereditary fructose intolerance |
| Fatty acid oxidation defect |
| Bile acid synthesis defects |
| Mitochondrial disorders, perinatal hemochromatosis, Nieman-Pick Type C |
| |
| **(ii) Toddler / Child** |
| Wilson disease |
| Mitochondrial disorders |
| Alpha 1 Anti Trypsin deficiency |
| Reye Syndrome |
| Nieman-Pick Type C |
| |
| **(iii) Adolescent** |
| Wilson disease |
| Fatty liver of pregnancy |
| Nieman-Pick type C |
| |
| **2. Infections (8% of Paediatric Acute Liver Failure)** |
| **(i) Infants** |
| Hepatitis A virus |
| Hepatitis B virus |
| Non A Non B hepatitis |
| Adenovirus |
| EBV |
| Echovirus |
| Coxsackie virus |
| |
| **(ii) Toddler / Child, Adolescent** |
| Adenovirus |
| Varicella Zoster virus |
| Epstein Barr virus |
| Cytomegalovirus |
| Paramyxovirus |
| Influenza virus |
| Hepatitis A virus |
| Hepatitis B virus |
| Non A Non B hepatitis |
| |

| **3. Vascular / Ischemic** |
|---|
| **(i) Infants** |
| Myocarditis |
| Severe asphyxia |
| Cardiac surgery |
| Congenital heart disease |
| |
| **(ii) Toddler/Child, Adolescent** |
| Budd- Chiari syndrome |
| Myocarditis |
| Post-operatively |
| Cardiomyopathy |
| |
| **4. Drugs / toxins (12% of Paediatric Acute Liver Failure)** |
| **(i) Infants** |
| Paracetamol |
| Valproate |
| Trimethoprin / sulfamethoxazole |
| |
| **(ii) Toddler / Child, Adolescent** |
| Paracetamol |
| Valproate |
| Antibiotics (trimethoprim / sulfamethoxazole, rifampicin, lisinopril, heliotrope, mushrooms, senecio |
| |
| **5. Autoimmunity (7% of Paediatric Acute Liver Failure)** |
| **(i) Toddler / Child, Adolescent** |
| Autoimmune hepatitis |
| |
| **6. Malignancy** |
| **(i) Infants, Toddler / Child, Adolescent** |
| Haemophagocytic Lympho Histiocytosis |
| |

*Adapted from Acute Liver Failure in Children, Mouzaki, Ng. VoL. 11, No. 3 p198-206*

**APPENDIX 3**

## West-Haven Criteria for Hepatic Encephalopathy in Adult Acute Liver Failure

| Stage | Consciousness | Intellect and behaviour | Neurologic findings |
|---|---|---|---|
| 0 | Normal. | Normal. | Normal examination; if impaired psychomotor testing, then mHE. |
| 1 | Mild lack of awareness. | Shortened attention span; impaired addition or substraction. | Mild asterixis or tremor. |
| 2 | Lethargic. | Disoriented; inappropriate behaviour. | Obvious asterixis; slurred speech. |
| 3 | Somnolent but arousable. | Gross disorientation; bizarre behaviour. | Muscular rigidity and clonus; Hyper-reflexia. |
| 4 | Coma. | Coma. | Decerebrate posturing. |

## Grading of Hepatic Encephalopathy in Paediatric Acute Liver Failure

| Stage | Asterixis | EEG changes | Clinical manifestations |
|---|---|---|---|
| I *Prodomal* | Slight | Minimal | Mild intellectual impairment, disturbed sleep-wake cycle |
| II *Impending* | Easily elicited | Usually generalised slowing of rhythm | Drowsiness, confusion, coma, inappropriate behaviour, disorientation, mood swings |
| III *Stupor* | Present if patient cooperative | Grossly abnormal slowing | Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign |
| IV *Coma* | Usually absent | Appearance of delta waves, decreased amplitudes | Unconscious, decerebrate or decorticate; Response to pain,<br>- present (IV A)<br>- absent (IV B) |

**Abbreviation:**

PALF : Paediatric Acute Liver Failure
ULN: Upper limit of normal
HE: Hepatic encephalopathy
ICP: Intracranial pressure
MISC: Multisystem Inflammatory Syndrome in Children
RP: Renal profile
Ca: Calcium
Mg: Magnesium
PO4: Phosphate
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
ALP: Alkaline phosphatase
GGT: Gamma-glutamyl transferase
CMV: Cytomegalovirus
EBV: Ebstein Barr virus
HSV: Herpes Simplex virus
HHV: Human Herpes virus
PCR: Polymerase chain reaction
ESR: Erythrocyte sediment rate
BNP: Brain natriuretic peptide
ECG: Echocardiogram
CVP: Central venous pressure
SVR: Systemic vascular resistance
MARS: Molecular Absorbent Recirculating System