HEPATOLOGY SERVICES

A Guide for

Fellows and Residents

Updated:
March 30, 2007

Anne M. Larson, M.D.
Hepatology Section
Division of GI
Department of Medicine
**Overall:**
This is an overall schedule of the outpatient portion of our rotation. See individual section for complete view of duties.

<table>
<thead>
<tr>
<th>TIME</th>
<th>MONDAY</th>
<th>TUESDAY</th>
<th>WEDNESDAY</th>
<th>THURSDAY</th>
<th>FRIDAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>GI/Hep Fellows Other Training</td>
<td>8:30 Liver Tx Clinic (preOLT)</td>
<td>8:30 Liver Tumor Clinic</td>
<td>Medicine Grand Rounds</td>
<td>7:30-10:00 GI Conf.</td>
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<td>9:00</td>
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<td>Surgery Pavilion Surgery Clinic</td>
<td>Genome Sci Bldg Rm 060</td>
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<td>10:00</td>
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<td>10:00 Liver Tumor Conference NE110 - 1st floor</td>
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<tr>
<td>1:00</td>
<td>1:00 Hepatology Clinic (new pts)</td>
<td>1:00 Liver Tx Clinic (newOLT)</td>
<td>12:30 Hepatology Clinic (new pts)</td>
<td>1:00 Liver Tx Clinic (postOLT)</td>
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<tr>
<td>2:00</td>
<td>8SE Clinic</td>
<td>8SE Clinic</td>
<td>Med Specialties</td>
<td>Med Specialties</td>
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<td>3:00</td>
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<tr>
<td>4:00</td>
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<td>Biopsy (path) Conf. NE110 - 1st floor</td>
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<td>5:00</td>
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</tbody>
</table>

Tx and OLT = transplant
People to Know

People to Know:

- **Liver Transplant Nurses & Coordinators** - an abundance of information!!
  - Mary Kester RN - x84838; beeper 541-4077; Fax x85976; Room EE-419
  - Jennifer Boyer RN - x84506; beeper 559-2648; Fax x85976; Room EE-419
  - Christine Ocampo RN - x80554; beeper 540-9634; Fax x85334; Room EE-413
  - Mark Baglien RN - x84780; beeper 560-0663; Fax 85334; Room EE-413

- **Patient Care Coordinators**
  - Charles Calhoun (hepatology) - x82217; room EE405
  - Colleen Berard (transplant) - x80549; beeper 540-1868; fax x83551; room EE405
  - Joann Williams (transplant) - x80017, beeper 541-8833, fax x83551; room EE405
  - Jan Thomas (tumor) - x80539, beeper 598-8600, fax x85334; room EE417

- **Medical Assistants - Liver Care Line**
  - Dorothy Rush - x87580; fax x85627
  - Michelle Corwin - x86658; fax x85627
  - Zahra Ali - x84615; x82105

- **Nurse Practitioners/Physicians Assistants**
  - Marie Hawley ARNP - x82595; beeper 541-9251; room EE417
  - Sean Rossiter PA-C - x84781; beeper 541-6668; room EE417
  - Tony Mitchell ARNP - x82368; beeper 540-7501; fax 88119; room EE417

- **Assistants**
  - Jodi Naylor - x84908; fax x83884 - Liver Care Line Program Coordinator
SENIOR HEPATOLOGY FELLOW

Basics:

• Hepatology Biopsy Beeper: 626-1739
• Fellows' Office: EE-403
• Fellow's Pager: variable depending upon which fellow is on

Hepatology Fellow's Schedule

<table>
<thead>
<tr>
<th>Weekday</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>OTHER TRAINING MORNING</td>
<td>1-5 Hepatology Clinic† (8SE)</td>
</tr>
<tr>
<td>Tuesday</td>
<td>8:30-12:00 transplant Clinic† (8SE)</td>
<td>1:00-5:00 transplant Clinic† (8SE)</td>
</tr>
<tr>
<td>Wednesday</td>
<td>8-1:00 Liver Tumor Clinic†</td>
<td>4-5 pathology conference (NE110)†</td>
</tr>
<tr>
<td>Thursday</td>
<td>8-9 medicine grand rounds (optional)</td>
<td>12:30-5:00 Hepatology Clinic† **</td>
</tr>
<tr>
<td>Friday</td>
<td>7:30-9 GI edu. conf. (k-069)†</td>
<td>1-5 transplant Clinic† **</td>
</tr>
</tbody>
</table>

Tx = transplant † Required Attendance **medical specialties

Hepatology Consultations:

It is expected that the Hepatology Fellow ("the Fellow") would be able to direct the GI fellow and resident while on the Hepatology Service, and provide structure and teaching to the GI fellow and the Hepatology Resident. The Fellow is expected to aid the GI fellow and resident with consults, paracenteses, and liver biopsies if the GI fellow is overwhelmed with the volume.

• Inpatient - Inpatient consults are performed by the R3 and reviewed by the Attending and team on rounds. If the R3 is overwhelmed or is absent, consults are done by the GI fellow with backup from the Fellow.
• DICTATIONs - initial inpatient consultation notes should be dictated. The dictation code for an inpatient consultation is 39 and the Hepatology code is 58.
• DAILY NOTES ON ALL HEPATOLOGY CONSULTATIONS UNTIL OFFICIALLY SIGNED OFF (unless there is really nothing new to add to the case).

• Outpatient - Occasionally, (rare) there will be the need to see a patient outside of the regular clinic hours. The timing of these consultations will be worked out by you and the coordinators. The dictations codes for an outpatient Hepatology OR Liver Transplantation consultation are 30 and the Hepatology code is 58.

• Paracentesis - Non-transplant (hepatology) patients requiring frequent paracentesis are usually admitted to 4-South and we perform the paracentesis there. They are then discharged to home. We are sometimes asked to do paracentesis on these patients. This should be pre-arranged with the GI fellow and the R3. There are paracentesis kits on the floor.
Transplant Patients:

- **Outpatients** are managed by the Liver Transplant Nurse Coordinators in conjunction with the MDs. The nurses may come to the Fellow with questions about patient management. Please be as promptly responsive as possible. They are great to work with, and save you a lot of work. (see below for names and numbers

- **Inpatients** - Depending on their transplant activation status, patients are handled differently:
  - **Pre-Activation** - admitted to medicine service and handled as a consultation (daily notes)
  - **Activated** - admitted to the transplant. Hepatology rounds daily with the transplant team and the Fellow is welcome to attend.
  - **Initial Post-Transplantation** - admitted to the transplant service and followed closely by us. Hepatology rounds daily with the transplant team on these patients.
  - **Post-Transplantation in Rehab** - all patients transferred to the Rehab service after their liver transplant are followed daily by the hepatology service (daily notes) with transplant surgery consultation as needed.
  - **Post-Transplantation long term** - patients who are far out from their transplant (i.e., >6 months) with medical issues generally go to transplant.
  - **Sick / Pre-Activation** - patients requiring intensive care, are admitted to the ICU team and are followed by us as a consultation (daily rounds; daily notes)
  - **Sick / Activated** - patients requiring intensive care, are admitted to the ICU team and are followed by us as a consultation (daily rounds)
  - **Transplant Evaluations (In-Patient)** - will be tailored based on the patient's acuity.
  - **Paracentesis** - Pre-transplant patients requiring frequent paracentesis are usually admitted to 4-South and we perform the paracentesis there. They are then discharged to home. We may be asked to do paracentesis on liver transplant patients - this we do if the surgical transplant residents are overwhelmed. There are paracentesis kits on 4-South and 4-SE.

Rounding with the Liver Transplantation Team daily:

It is not expected that the Fellow will have primary responsibility for patients on the Liver Transplantation Service (such as writing daily notes and follow-up on laboratory tests, etc.). It is expected that the Fellow will be an active participant in daily transplant rounds. The Fellow will be able to meet criteria for UNOS certification as a transplant hepatologist at the conclusion of a full year because of these activities.

Liver Selection Conference:

It is recommended that the Fellow attend several of these sessions during the year to obtain an education on the process of selection of patients for liver transplantation. This is the meeting at which potential candidates are discussed and decisions are made regarding whether to accept them as a transplant patient. Generally, this presentation is done by the GI Fellow. Occasionally, depending on the GI Fellow's clinic schedule, the Fellow will be asked to present the pre-transplant patients (usually 2-10 cases) to the Committee at this meeting. Try to get the charts from the transplant coordinators by Monday - it helps to keep you from getting backed up.
Call:
The Fellow will be expected to take transplant/hepatology call in rotation with GI. Call consists of seeing sick inpatient Hepatology Consults, and taking all new Hepatology consultations that may be requested.

Clinics:
This is the mainstay of the Hepatology service. These clinics tend to be very popular with the fellows and the residents. There are many interesting cases that are seen. In order to be fully trained in all aspects of liver disease and academic research, the Fellow is expected to attend all clinics:

- Liver Transplant Clinics - Tuesday; our busiest clinic and Friday afternoon
- Hepatology Clinics - Monday afternoon and Thursday afternoon
- Liver Tumor Clinic - Wednesday mornings (in the Surgery Pavilion)

All new patients seen in the clinics must have a full note dictated as well (page 24). It is important to get the title of the note correct. The hepatology clinic notes should be entitled:

- HEPATOLOGY CLINIC - INITIAL CONSULTATION
- LIVER TRANSPLANT CLINIC - INITIAL CONSULTATION
- LIVER TUMOR CLINIC - INITIAL CONSULTATION.

This is very helpful when looking back to see if a patient has been seen in transplant or hepatology clinic. Is it even more helpful when a patient comes into the ER - allowing the ER physicians to appropriately determine who to call.

Division-wide Programs:
It is expected that the Fellow will participate in the GI Division-wide education programs designed for the fellows and faculty members.

Pathology Conference:
It is expected that the Fellow attend the weekly pathology conference to evaluate all liver biopsies performed. This is an extremely valuable educational tool and imperative for any physician wishing to become a Hepatologist/Transplant Hepatologist.

Gut Course:
Occasionally, the Fellow is asked to assist in teaching the Gut Course. This is the course given to the second year medical students as their introduction to gastroenterology. It is exciting and well received by the students.

Phone Calls:
There are a significant number of "communication" telephone calls with referring physicians. These are often routed to the fellow by the coordinators and the operators. If the fellow is uncomfortable fielding any particular call, let your attending know. Calls coming through the Medical Consultation (MedCon) service are generally sent to the attending.
**GI FELLOW**

**Basics:**
- Hepatology Biopsy Beeper: 626-1739
- GI Fellows' Office: EE-403
- Senior Hepatology Fellow’s Pager: variable

**GI Fellow’s Schedule**

<table>
<thead>
<tr>
<th>Weekday</th>
<th>AM</th>
<th>PM</th>
</tr>
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<tbody>
<tr>
<td>Monday</td>
<td>OTHER TRAINING MORNING (clinician-teachers only)</td>
<td>1:00 hepatology clinic %†</td>
</tr>
<tr>
<td>Tuesday</td>
<td>8:30-12:00 transplant clinic %†</td>
<td>1:00-5:00 transplant clinic %†</td>
</tr>
<tr>
<td>Wednesday</td>
<td>liver biopsies (~5-7)</td>
<td>12:30 selection conference (EE424) †</td>
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<td>10-11 hepatoma conference (optional)*</td>
<td>4-5 pathology conference † (NE110)</td>
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<tr>
<td>Thursday</td>
<td>8-9 medicine grand rounds (optional)</td>
<td>12:30 hepatology clinic †‡</td>
</tr>
<tr>
<td></td>
<td>liver biopsies (~3-4)</td>
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<tr>
<td>Friday</td>
<td>7:30-9 educational conference (K-069)</td>
<td>1:00-5:00 transplant clinic †‡</td>
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<td></td>
<td>9-10 ICU/transplant rounds*</td>
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<tr>
<td></td>
<td>liver biopsies (~3-4)</td>
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</tbody>
</table>

*Optional (but if you’re interested, we’d love to have you!)* † Required Attendance
% 8-Southeast Clinic ‡ 3rd Floor - Medical Specialties

**Liver Biopsies:**
- **Who** - Done by the GI Fellow
- **Where** - Biopsies should be done before noon if at all possible (exception - on days with AM clinics or other training morning). Patients undergo ultrasound and are “marked”. They will be returned to one of the floors (4S, 7S or 4SE). The ultrasound technologists will page when the patients are sent back to the floor and code the patient's floor into the beeper. Generally, they will code “6211-4” and this means that they have sent the patient back to the 4th floor. If there is anything complicated or unusual going on, they will just page you to 6211. This page you should answer. The floor may also page you with patient arrival.
- **Schedule** is kept by Joann Williams (EE-405) - 598-0017 beeper 541-8833
- **Outpatient Biopsies**
  - Hepatology - scheduled by Hepatology patient care coordinator (PCC) (x82217)
  - Research Patients - scheduled by research coordinators
  - Transplant - scheduled by transplant patient care coordinators (Joanne Williams x80017)
- **Inpatient Biopsies** (usually post-transplant protocol biopsies). Inpatients are scheduled **by the GI fellow and the Liver Transplant service** (DON’T FORGET TO CALL ULTRASOUND x86211 if...
Transplant surgeons don’t and DON’T FORGET TO WRITE PRE- AND POST-BIOPSY ORDERS). Let Joanne know about inpatient biopsies so they can be recorded in the schedule book. Joanne has preprinted order forms for these situations.

- **Liver Donors** - The GI Fellow may occasionally receive a call from Life Center Northwest to perform a liver biopsy on a donor for liver transplant at the UW or another hospital. This biopsy is essential to assess whether the liver is acceptable to use for transplantation. This is one of the Hepatology Service’s duties after 5 pm and on weekends. This should not be referred to the GI service at the outside institution. During the daytime, we can’t do this, so it can be referred to the GI service from 8 am to 5 pm.

- **Pre-Biopsy** - obtain PT/PTT/CBC/platelets results (usually ordered at the time of scheduling of the biopsy) and informed consent prior to biopsy. Mild sedation (i.e., 1–2 mg of Ativan) is OK for nervous patients (obtain informed consent prior to sedation).

- **Types of Biopsies:**
  - A **RUSH** ("same day") biopsy is an urgent clinical case that requires a same day diagnosis AND can be delivered to the Pathology lab before 12 NOON. A diagnosis will be called to the submitting clinician by 7 PM that day.
  
  - A **FRIDAY RUSH** is a biopsy that requires a Saturday diagnosis. These are usually done if rejection is of concern. Please call the pathology fellow and pathology attending (598-6400 or 598-6190) to let them know that a diagnosis is needed on Saturday.

  - An **URGENT** ("next day") biopsy is an urgent clinical case that cannot be delivered to Pathology by 12 Noon. This will still be expedited if it is submitted by 6:00 PM. The results will be called back to the submitting clinician the following day. Please indicate the need for a next day report on the biopsy accession form.

  - All **NON-URGENT** ("Routine") biopsies will be processed routinely by Pathology. Only unexpected diagnoses of rejection will be telephoned to the clinician. All other diagnoses should be available on the afternoon of the third working day after the biopsy.

  - A biopsy for **IRON MEASUREMENT**. A SEPARATE piece of the liver tissue will be sliced off and placed in a red top tube. This, along with the yellow form labeled "Clinical Lab Request" should be taken to the SPS (Specimen Processing Services) Lab on the 2nd floor NW220 (down the hall from the Gross room) or Tube stop 11.

- **Recording the Results**
  - Routine results will be available by the third or fourth day on the computer.
  - Track down anything else you may need (Drs. Yeh, x80008 or Upton x800063; Path, x86400)
  
  - **All biopsies must be dictated as a procedure.**
    - There’s a template (See Page 16). When you dictate, let them know the date of service and then tell them to use the "liver biopsy glossary." Only spaces marked with ?? need to be dictated.

  - Go over the actual slides with pathologist at Pathology Conference (Wednesday: 4:00-5:00)
• **Biopsy Follow-up**
  - Patients are instructed to make a follow-up appointment with their Hepatologist in the clinic following the liver biopsy to go over their biopsy results. **DO NOT** TELL THE PATIENT THAT SOMEONE WILL CALL THEM WITH BIOPSY RESULTS OR THAT THEY SHOULD CALL FOR THEIR RESULTS.

• **Other Information**
  - A pathology technician is available on call 7-9 pm Monday through Friday, 8am to 9 pm Saturdays, and 4-9 pm Sundays. Pager is 340-3725. See page 26 for a summary of liver biopsy risks and their occurrence.

**Hepatology Consultations:**

• **Inpatient** - Inpatient consults are performed by the R3 and reviewed by the Attending/team on rounds. If the R3 is overwhelmed/absent, consults are done by the GI fellow with backup from the Hepatology Fellow.
  - **DICTATIONs** - INPATIENT INITIAL CONSULTATION NOTES SHOULD BE DICTATED. The dictation code for an inpatient consultation is 39 and the Hepatology code is 58.
  - **DAILY NOTES** SHOULD BE WRITTEN ON ALL HEPATOLOGY CONSULTATIONS UNTIL OFFICIALLY SIGNED OFF (unless there is nothing new to add to the case).

• **Outpatient** - Occasionally, (rare) there will be the need to see a patient outside of the regular clinic hours. The timing of these consultations will be worked out by you and the coordinators. The dictations codes for an outpatient Hepatology OR Liver Transplantation consultation are 30 and the Hepatology code is 58.

• **Paracentesis** - Non-transplant (hepatology) patients requiring frequent paracentesis are usually admitted to 4-South and we perform the paracentesis there. They are then discharged to home. We are sometimes asked to do paracentesis on these patients. This should be pre-arranged with the GI fellow and the R3. There are paracentesis kits on the floor.

**Transplant Patients and Workup:**

• **Outpatients** are managed by Transplant Nurse Coordinators in conjunction with the MDs. The nurses may come to you with questions. Please be as promptly responsive as possible. They are great to work with, and save you a lot of work. (see names below)

• **Inpatients** - Depending on their transplant activation status, patients are handled differently:
  - **Pre-Activation** - admitted to medicine service and handled as a consultation (daily notes)
  - **Activated** - admitted to the transplant. Hepatology rounds daily with the transplant team and the Fellow is welcome to attend.
  - **Initial Post-Transplantation** - admitted to the transplant service and followed closely by us. Hepatology rounds daily with the transplant team on these patients.
  - **Post-Transplantation in Rehab** - all patients transferred to the Rehab service after their liver transplant are followed daily by the hepatology service (daily notes) with transplant surgery consultation as needed.
• **Post-Transplantation long term** - patients who are far out from their transplant (i.e., >6 months) with medical issues generally go to transplant.

• **Sick / Pre-Activation** - patients requiring intensive care, are admitted to the ICU team and are followed by us as a consultation (daily rounds: daily notes)

• **Sick / Activated** - patients requiring intensive care, are admitted to the ICU team and are followed by us as a consultation (daily rounds)

• **Transplant Evaluations** (In-Patient) - will be tailored based on the patient’s acuity.

• **Paracentesis** - Pre-transplant patients requiring frequent paracentesis are usually admitted to 4-South and we perform the paracentesis there. They are then discharged to home. We may be asked to do paracentesis on liver transplant patients - this we do if the surgical transplant residents are overwhelmed. There are paracentesis kits on 4-South and 4-SE.

**Liver Selection Conference:**

This is the meeting at which potential candidates are discussed and decisions are made regarding whether to accept them as a transplant patient. You will be asked to present the pre-transplant patients (usually 2-10 cases) to the Committee at this meeting. Try to get the charts from the transplant coordinators by Monday - it helps to keep you from getting backed up. The meeting is held on Wednesdays at 12:30 in the transplant conference room (EE-424).

• **Current Transplant Candidacy Status.**

  • **Status 1** - A patient greater than or equal to 18 years of age with fulminant liver failure with a life expectancy without liver transplant of less than 7 days. This includes:

    • **Fulminant hepatic failure** defined as the onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease. The absence of pre-existing liver disease is critical to the diagnosis. While no single clinical observation or laboratory test defines fulminant hepatic failure, the diagnosis is based on the finding of stage II encephalopathy (i.e., drowsiness, inappropriate behavior, and incontinence with asterixis) in a patient with severe liver dysfunction. Evidence of severe liver dysfunction may be manifest by some or all of the following symptoms and signs: asterixis (flapping tremor), hyperbilirubinemia (i.e., >15 mg/dL), marked prolongation of the PT (i.e., >20 sec or INR >2.5), or hypoglycemia; or.

    • primary non-function of a transplanted liver within 7 days of implantation; or
    • hepatic artery thrombosis in a transplanted liver within 7 days of implantation; or
    • acute decompensated Wilson’s disease;

  • **All Other** - All other patients will be assigned a mortality risk score calculated in accordance with the MELD (model of end stage liver disease) scoring system

    \[
    MELD = 0.957 \times \log_{e}(\text{creatinine mg/dL}) + 0.378 \times \log_{e}(\text{bilirubin mg/dL}) + 1.120 \times \log_{e}(\text{INR}) + 0.643.
    \]

    The maximum MELD score will be 40.

    • **Creatinine.** The maximum creatinine considered will be 4.0 mg/dL. For patients on dialysis (2 or more treatments per week) the creatinine will automatically be set at 4.0 mg/dL.

    • **Lab Values:** Laboratory values less than 1.0 will be set to 1.0 for the purpose of the calculation.
• **Waiting Time**: In patients with identical MELD score, the patient who has waited longest will receive the next available liver.

• **Hepatocellular Carcinoma**: A patient with HCC and a tumor that is ≥3 cm will be listed with a MELD score equivalent to a 20% probability of death within 3 months. A patient with and HCC ≥3 cm may be listed at a MELD score equivalent to 40% probability of death within 3 months. Patients will receive additional MELD points equivalent to a 10% increase in pre-transplant mortality every 3 months until they receive a transplant or are determined to be untransplantable.

• **Exceptional Cases**: Special cases require prospective review by the Regional Review Board, which will accept or reject the request for listing. Exceptions must be reapplied every 3 months.
  - **Hepatopulmonary Syndrome**: Evidence of portal HTN, evidence of a shunt, and a PaO₂ <60 on room air.
  - **Familial Amyloidosis**.
  - **Primary Omaluria**.

• **Status 7**: temporarily inactive, however, the patient continues accruing waiting time up to a maximum of 30 days. Patients who are considered to be temporarily unsuitable transplant patients (i.e., infected) will be listed as status 7, temporarily inactive.

**Call**:

The GI Fellow takes call on weeknights during the month. Most of these you can handle by yourself, but the attending should be called for major decisions. **The fellow should never accept a patient in transfer without first discussing with the attending.** Call for the weekend is based upon the GI call schedule—there is always hepatology attending backup. Weekend call consists of seeing sick inpatient Hepatology Consults, and taking all new Hepatology consultations that may be requested.

**Transfers**:

You may receive calls from outside attending physicians regarding the possibility of bringing patients in for liver transplantation. Before accepting any patient, you need to run it by the Attending on service or on call (and the transplant coordinator if it is "for a transplant" [on call if necessary]). **We must never tell a referring doctor that we will accept someone for liver transplantation** (frequently they do not turn out to be transplant candidates once we've taken a look at them). The best thing to tell the outside physicians is that we'd be happy to accept them for consultation and evaluation and further management of their liver disease.

**Clinic**:

This is the mainstay of the Hepatology service. These clinics tend to be very popular with the fellows and the residents. There are many interesting cases that are seen.

- **Hepatology Clinics** - Monday afternoon and Thursday afternoon
- **Transplant Clinic** - all day Tuesday - our busiest clinic, and Friday afternoon

All new patients seen in the clinics must have a full note dictated as well (page 24). **It is important to get the title of the note correct.** The hepatology clinic notes should be entitled:
• HEPATOLOGY CLINIC - INITIAL CONSULTATION
• LIVER TRANSPLANT CLINIC - INITIAL CONSULTATION
• LIVER TUMOR CLINIC - INITIAL CONSULTATION.
This is very helpful when looking back to see if a patient has been seen in transplant or hepatology clinic. Is it even more helpful when a patient comes into the ER - allowing the ER physicians to appropriately determine who to call.

**Responsibilities:**
In addition to the above, the GI Fellow essentially “runs” the consult service and floor service. This means working closely with the R3 on those consultations we do have, and working with the Transplant Service on our transplant patients. Rounds occur at 4:00 every evening and should be attended by the GI Fellow (they are optional for the R3). Full Review of Systems and Physical Exams must be dictated.
PROCEDURE:
Percutaneous liver biopsy

PROCEDURE CODE:
47000

INDICATIONS:  

OPERATORS:  

ANESTHESIA:
Local 1% lidocaine

INFORMED CONSENT:
The procedure, its indications, potential complications (including, but not limited to, discomfort, bleeding, infection, puncture of other organs, death, misdiagnosis), and the alternatives available were explained to the patient, who appeared to understand and indicated this. An opportunity for questions was provided and informed consent was obtained.

DESCRIPTION
Ultrasound was used to locate the appropriate biopsy site. The skin was locally cleansed with Betadine and prepared in sterile fashion. 1% Lidocaine was used to locally anesthetize the skin, subcutaneous tissues, muscles and diaphragm. With the patient in the end-expiratory position, a 15-gauge Klatskin needle and the standard Menghini technique was used to obtain an adequate specimen on  pass/passes. The patient tolerated the procedure well and there were no immediate complications.

The attending physician, Dr. was present throughout the entire procedure.
HEPATOLOGY R3

Basics:

- GI Fellow Biopsy Beeper: 626-1739  GI Fellows'/Resident's Office: EE-403 (temporary)
- Senior Hepatology Fellow's Pager: variable, see schedule

Resident's Schedule

<table>
<thead>
<tr>
<th>Weekday</th>
<th>AM</th>
<th>PM</th>
</tr>
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<tbody>
<tr>
<td>Monday</td>
<td>8:30-12:00 transplant clinic%†</td>
<td>1:00-5 hepatology clinic%†</td>
</tr>
<tr>
<td>Tuesday</td>
<td>8:30-12:00 transplant clinic%†</td>
<td>1:00-5:00 transplant clinic%†</td>
</tr>
<tr>
<td>Wednesday</td>
<td>10-11:30 liver tumor conference (optional)*</td>
<td>1-3 selection conference (EE424)*</td>
</tr>
<tr>
<td></td>
<td>9-10 ICU/transplant rounds*</td>
<td>4-5 pathology conference (NE110)*</td>
</tr>
<tr>
<td>Thursday</td>
<td>8-9 medicine grand rounds</td>
<td>12:30-5:30 hepatology clinic†</td>
</tr>
<tr>
<td></td>
<td>9-11:00 residents teaching conferences</td>
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</tr>
<tr>
<td>Friday</td>
<td>7:30-10 GI educational conference*</td>
<td>1:00-5 transplant clinic†</td>
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</tbody>
</table>

*Optional (but if you're interested, we'd love to have you!)  %8-Southeast Clinics  † Required attendance  $Clinics are in Med Specialties

Responsibilities:

- **Call** - The resident does not take Hepatology call.
- **Clinics** - This is the mainstay of the Hepatology service. These clinics tend to be very popular with the fellows and the residents. There are a lot of interesting cases that are seen:
  - **Hepatology Clinics** - Monday afternoon and Thursday afternoon. Attendings are: Drs. Carithers, Larson, Kowdley, and Tung
    - See 3-4 new patients referred for hepatology consultation
    - These patients can be extremely varied and interesting. We'll try to let you see a variety of diseases.
  - **Transplant Clinic** - all day Tuesday - our busiest clinic, and Friday afternoon. Attendings are: Dr. Carithers, Kowdley, Larson, Tung, Transplant Surgeons
    - See 2 to 5 new patients referred for liver transplant workup.
    - See listed and long-term follow-up patients.

All new patients seen in the clinics must have a full note dictated as well (page 24). **It is important to get the title of the note correct.** The hepatology clinic notes should be entitled:
  - HEPATOLOGY CLINIC - INITIAL CONSULTATION
  - LIVER TRANSPLANT CLINIC - INITIAL CONSULTATION
  - LIVER TUMOR CLINIC - INITIAL CONSULTATION.
This is very helpful when looking back to see if a patient has been seen in transplant or hepatology clinic. Is it even more helpful when a patient comes into the ER - allowing the ER physicians to appropriately determine who to call.

- **Daily**
  - Hepatology consults on all non-transplant patients (we don't get too many of these). These patients need to be seen daily with notes written. *This should be done early if possible because the afternoons often leave little time for rounding.*
  - Transplant patients on the Rehabilitation Service are followed by us and should have daily notes written.
  - Round on any pre-transplant (non-listed) patients daily when they're on the medicine service (except weekends). *This should be done early if possible.*
    - We'll try to help the transplant service manage these patients.
    - If you don't have time to see the patients, let the GI fellow know early.
    - The GI Fellow will also help you with these duties if you feel overwhelmed.
  - Help coordinate interactions between transplant service and medicine.

- **Liver Transplant Evaluation Conference** - this is held on Wednesdays at 12:30 in EE424. It is not mandatory that you attend, but you may find it interesting and informative regarding the process of patient acceptance as a transplant candidate.

- **Weekends** - The R3 has all weekends off while on the hepatology service! (There may be some inpatient coverage required by the department of medicine.)

- **Hepatology Consultations:**
  - **Inpatient** - Inpatient consults are performed by the R3 and reviewed by the Attending and team on rounds. If the R3 is overwhelmed or is absent, consults are done by the GI fellow with backup from the Fellow.
  - **Dictations** - inpatient consultation notes should be dictated. The dictation code for an inpatient consultation is 39 and the Hepatology code is 58.
  - **Daily notes should be written on all Hepatology Consultations until officially signed off** (unless there is nothing new to add to the case).

- **Outpatient** - Occasionally, (rare) there will be the need to see a patient outside of the regular clinic hours. The timing of these consultations will be worked out by you and the coordinators.

- **Paracentesis** - Pre-transplant or hepatology patients requiring frequent paracentesis are usually admitted to 4-South and we perform the paracentesis there. They are then discharged to home. We are frequently asked to do paracenteses on the transplant patients - this we do because the surgical transplant residents are generally overwhelmed.

**Liver Transplant Workup:** - what does it entail?

- **Labs** - Liver Transplant Panels 1-4 - ordered as LTXW1, LTXW2, LTXW4 (includes M7, CBC, LFTs, viral and fungal serologies, coags, Fe-studies, alpha-1 antitrypsin, alpha-fetoprotein, etc.). Urinalysis needs to be
ordered separately. Blood also needs to be sent to the Puget Sound Blood Center for "ABO, Rh, and antibody screen"

- 24 hour urine for creatinine clearance and protein
- **Abdominal CT** - order as "**pre-liver transplant**"
  - with and without contrast if renal function is ok
  - MRI/MRA is done if creatinine is >1.2
- **ECHO / EKG**
- **CXR**
- **ABG**
- **PPD**
- Dental examination
- Social Work evaluation
- Dietary/Nutrition consult
- Vaccinations
- Mammogram and Pap Smear
- 3-Hour Patient Education classes
- Financial clearance
- **As Warranted:**
  - Cardiology consult
  - Abdominal ultrasound (special attention to portal vein to r/o thrombosis)
  - Upper endoscopy
  - PFTs
  - Pulmonary consult
  - Infectious disease consult
  - Anesthesia consult
  - Bone densitometry
  - Stress thallium (all patients >50 years of age)
  - Surveillance colonoscopy (all patients >50 years of age)

- **Emergent Transplant** - if the pre-transplant evaluation is deemed emergent, the essential components of the work-up are the labs, ECHO, and abdominal ultrasound (it's important to know this if you are on call and a fulminant liver failure comes in). Social work evaluation and financial clearance are essential. **IMPORTANT:** Anytime a liver transplant evaluation is being considered, contact the transplant coordinator. After hours, contact the "transplant coordinator on-call" through paging. They will initiate early contact with the social worker and financial counselor. Most of this will be done by the Hepatology Fellow on call.
OVERALL EDUCATIONAL PURPOSE

1. Liver Disease. To learn to recognize and treat the major clinical syndromes and diseases encountered in the practice of hepatology, including, but not limited to:
   - Acute Liver Failure
   - Alcoholic Liver Disease
   - Autoimmune Liver Diseases, including
     - Autoimmune Hepatitis
     - Primary Biliary Cirrhosis (PBC)
     - Primary Sclerosing Cholangitis (PSC)
     - Overlap Syndromes
   - Budd-Chiari Syndrome
   - Drug-Induced Liver Disease
   - Liver Tumors, including:
     - Hepatocellular Carcinoma
     - Focal Nodular Hyperplasia
     - Hemangioma or Adenoma
   - Metabolic Liver Disease
     - Hemochromatosis
     - Wilson’s Disease
     - Alpha-1 Antitrypsin Deficiency
     - Nonalcoholic Steatohepatitis (NASH)
   - Viral Hepatitis

2. Liver Enzymes and Liver Function. To learn the appropriate assessment of elevated liver enzymes and their clinical implications.

3. Liver Transplant. To learn the appropriate testing necessary for assessment of and consideration for orthotopic liver transplantation.

4. Liver Biopsy. To learn appropriate use of liver biopsy. To learn liver histopathology and its interpretation to aid in clinical management.

5. TIPS. To learn the indications for TIPS placement and the assessment of patients TIPS (Transjugular Intrahepatic Portosystemic Shunt).

TEAM STRUCTURE

Hepatology Attending
1 Senior Hepatology Fellow
1 GI Fellow
1 R3
PRINCIPAL TEACHING METHODS

Case discussion and review
The hepatology attending, the hepatology fellow, and the GI fellow review and discuss all cases with the resident. All patients are seen by the attending.

Rounds
Rounds will be held daily or as needed on the Hepatology Consult patients. Bedside rounds are also held daily for patients on the liver transplant service. These are in conjunction with the Liver Transplant Surgeons.

Didactics in Liver
Weekly conferences are held including (1) departmental GI conference on a variety of topics including liver, (2) liver pathology conference during which all liver biopsies and liver transplants are reviewed, (3) liver transplant grand rounds, and (4) transplant residents lunch conference during which subjects directly related to transplant are discussed. Additionally, the Liver Transplant Selection Conference at which patients are discussed regarding their status for liver transplant may be informative to the resident regarding the process of patient acceptance as a transplant candidate.

Other Didactics
Residents are allowed to go to Residents’ report most days of the week as well as the Thursday morning Medicine Grand Rounds and residents’ lectures.

Observation
The resident will have the opportunity to observe liver biopsy and liver transplantation.

EDUCATIONAL CONTENT

Mix of Diseases
All of the diseases listed previously are seen, since the UWMC is a major referral center serving the WWAMI region. Hepatitis C is the most common entity seen, followed by the autoimmune and metabolic diseases.

Patient Characteristics
Patient characteristics are as varied as the number of liver diseases we see. Liver disease affects both genders and all ages.

Types of Clinical Encounters
• Clinics - The mainstay of Hepatology. These clinics are very busy and popular with the fellows and the residents. There are a lot of interesting cases:
  • Transplant Clinics – All day Tuesday (busiest) and Friday afternoon. Tuesday AM are patients listing and waiting for transplant. Tuesday PM, the resident sees 2 to 4 new patients referred for consideration of liver transplant. Friday afternoon is the long-term follow-up clinic where you will meet patients who’ve successfully undergone transplantation and are anywhere from 3 months to 15-20 years post-transplant.
  • Hepatology Clinic – Monday and Thursday afternoons. The resident sees 3-4 new patients referred for hepatology consultations. These patients are varied and interesting.
• Daily Consultations – The Hepatology service performs consults on all non-liver transplant patients. Liver transplant patients who are residing on the Rehabilitation Service are followed by the service as well.

Procedures
• Paracentesis – Pre-transplant or hepatology patients requiring frequent paracentesis are usually admitted to 4-South (short stay ward) and we perform the paracentesis there. They are then discharged to home. We are frequently asked to do paracenteses on the transplant patients – this we do because the surgical transplant residents are generally overwhelmed.

Services
The Hepatology Division offers a full range of services, some in conjunction with other divisions in the hospital
• Hepatic Consultation and Liver Biopsy Interpretation – Patients are offered expert consultation, including evaluation of complex liver biopsies.
• **Diagnostic Evaluation of Hepatitis C** – Using sophisticated diagnostic tests, patients can receive the most complete evaluation available for hepatitis C infection.

• **Therapy for Chronic Viral Hepatitis Infections** – The physicians at the UW are considered experts in the management of chronic Hepatitis B and C. There are many Hepatitis B and C clinical treatment trials ongoing at the UW.

• **Transjugular Intrahepatic Portosystemic Shunts ("TIPS")** – Patients with portal hypertension who have failed sclerotherapy/banding and who are referred to the UW Hepatology service have access to placement of a transjugular intrahepatic shunt by the Radiology Department.

• **A Comprehensive Evaluation and Treatment of Hepatobiliary Malignancies** – Patients are provided comprehensive evaluation and treatment of hepatobiliary malignancies ranging from surgical resection and chemotherapy to liver transplantation. There is no other such comprehensive service available in the region. The multidisciplinary group meets weekly, and includes Hepatologists, Hepatobiliary/GI Surgeons, Transplant Surgeons, Radiologists, Oncologists, and Pathologists.

**Rotation Specific Schedule**  **"** denotes Hepatology-specific events

**Monday**  
**Liver Transplant Rounds:** 9:00-11:00am, in MICU (optional for R3)  
Residents’ Report: 10:30-11:30am, medicine library  
Lunch Conference: 12:30-1:30pm, RR110  
**Hepatology Clinic:** 1:00-5:00pm; 8-Southeast clinic  

**Tuesday**  
**Liver Transplant Clinic:** 8:30am to 5:00pm; liver transplant clinic (8th Southeast)  

**Wednesday**  
**Liver Transplant Rounds:** 9:00-11:00am, in MICU (optional for R3)  
**Liver Tumor Clinic and Conference:** 8:00-12:30am (optional for R3)  
Residents’ Report: 10:30-11:30am, medicine library  
Lunch Conference: 12:30-1:30pm, RR110  
**Transplant Selection Conference:** 12:30-2:30pm, room EE-424 (optional for R3)  
**Pathology Conference:** 4:00-5:00pm; room NE110  

**Thursday**  
**Medicine Grand Rounds:** 8:00-9:00am, HSB T-625  
**Liver Transplant Rounds:** 9:00-11:00am, in MICU (optional for R3)  
**Residents’ Teaching Conference:** 9:15-10:15am, HSB T-739  
**Hepatology Clinic:** 12:30-5:30pm, medical specialties clinic  

**Friday**  
**GI Conferences:** 7:30-9:00am, K-069 (optional for R3)  
**Liver Transplant Rounds:** 9:00-11:00am, in MICU (optional for R3)  
Residents’ Report: 10:30-11:30am, medicine library  
**Transplant Residents Lecture:** 12:00-1:00pm, room EE-424  
**Liver Transplant Clinic:** 1:00-5:00pm, medical specialties clinic  

**Call and Weekend Responsibilities**  
The Hepatology consult resident will not be taking ICU call (as in previous years); however, s/he will be covering ICU Float and Medicine Float two weekends each month. Therefore, every other Monday the R3 will not be available to the consult services as they will have this day off.

**Principle Educational Materials Used**  

**Recommended Readings**  
There are many major hepatology texts and journals in the attendings’ offices. There is also a liver transplant library available in the Liver Transplant section.

**Pathologic Materials**  
While no specific teaching file is available, the pathology conferences reveal a plethora of histologic material.
METHODS USED IN EVALUATING RESIDENT AND PROGRAM PERFORMANCE.

At the end of the rotation, the resident is evaluated in writing and their performance reviewed with them verbally by every attending and fellow he or she has interacted with for a significant amount of time. The evaluator rates the resident on a nine-point scale in each component of clinical competence (i.e., patient care, medical knowledge, practice based learning improvement, interpersonal and communication skills, professionalism, system-based learning, educational attitudes, leadership, overall clinical competence).

The resident is given the opportunity to evaluate in writing the quality of the curriculum and the extent to which the educational goals and objectives of the rotation have been met. The resident also evaluates the teaching competence of each attending and fellow with whom s/he has interacted for a significant amount of time.
HEPATOLOGY (or LIVER TRANSPLANT) CLINIC NOTE - INITIAL CONSULTATION

IDENTIFICATION/CHIEF COMPLAINT:
Mr. X is a 50-y/o man sent in consultation by Dr._____ for evaluation and recommendations regarding ______.

HISTORY OF PRESENT ILLNESS:
The patient was seen and examined in the presence of Dr. ______________
Must contain chronological development of the HPI and ≥4 of the following elements:
- Location - location of problem
- Duration - length of time patient has had the problem
- Quality - i.e., dull sharp, constant, stable, improving, worsening, acute, etc.
- Severity - description of the severity of the pain or symptoms
- Timing - onset and chronology of the problem (explain in chronologic order)
- Context - when/where problem occurs (i.e., pain at rest, )
- Modifying factors - what has patient done to obtain relief or makes it worse
- Associated signs and symptoms

PMHx - required
FHx - required
SHx - required

MEDICATIONS - required

ALLERGIES - required

REVIEW OF SYSTEMS - Must contain ≥10/14 of the following systems
You CAN identify and dictate each system (i.e., “CV-positive for ..., GI-negative, GU-negative, Respiratory-negative, etc.” -OR- “ROS negative for constitutional/ENT/GI, etc.” -OR- you CAN dictate the positives then say “remaining X-point ROS negative.”
YOU CANNOT dictate it as “review of systems negative.”

Systems and examples:
- Constitutional - e.g., weight loss, fever, no acute distress, sleep habits, etc.
- Eyes - e.g., glasses, pain, diplopia, itch, dryness, glaucoma, spots, twitching, etc.
- ENMT - e.g., hearing loss, vertigo, ringing, bleeding, pain, hay fever, lip lesions, teeth, etc.
- Cardiovascular - e.g., chest pain, dyspnea, syncope, pulse, hypertension, etc.
- Respiratory - e.g., wheezing, hemoptysis, asthma, cyanosis, shortness of breath, etc.
- GI - e.g., nausea, vomiting, heartburn, bowel habits, bloating, pain, ascites, etc.
- GU - e.g., dysuria, frequency, burning, incontinence, sexual difficulty, etc.
- Musculoskeletal - e.g., joint pain, muscle pain/cramps, fracture, injuries, swelling, etc.
- Skin - e.g., rash, moles, tumors, sores, scars, varicose veins, breast pain/lumps, etc.
- Neurology - e.g., syncope, dizziness, tremor, coordination, ataxia, tension, headache, etc.
- Psych - e.g., depression, anxiety, suicidal thoughts, emotional instability, memory, etc.
- Endocrine - e.g., excessive sweating, voice change, goiter, thirst, appetite, HRT, etc.
- Heme/Lymph - e.g., bruising, fatigue, enlarged glands, phlebitis, anemia, etc.
- Allergy/Immunology - e.g., itching, hives, medication allergies, hay fever, etc.
PHYSICAL EXAM:  
Exam MUST contain ≥8 of the following systems and ≥2 sub-elements must be dictated:

- **Constitutional** - BP, pulse, respiration, temperature, height, weight (any 3)
- **Eyes** - conjunctive, lids, pupils, irises, light/accommodation, fundus
- **ENT, Mouth** - external inspection, hearing, nasal mucosa, lips/teeth/gums, oropharynx
- **Neck** - supple, lymphadenopathy, thyromegaly
- **Respiratory** - respiratory effort, percussion, palpation, auscultation
- **Cardiovascular** - palpation, auscultation, carotids, arteries for bruits, all pulses
- **Chest (breasts)** - inspection, palpation
- **GI** - describe abdomen, masses, tenderness, liver, spleen, hernias, anus, perineum, rectum
- **GU** - scrotal, penis, prostate, pelvic exam
- **Lymphatic** - (≥2 areas) neck, axilla, groin, other
- **Musculoskeletal** - (≥1 areas) head/neck; spine/ribs/pelvis, extremities (each counts as 1)
- **Skin** - inspection/palpation for rashes, lesions, ulcers, induration, nodules, etc.
- **Neurologic** - cranial nerves, deep tendon reflexes, sensation
- **Psychiatric** - judgment/insight, orientation, memory, mood, affect

LABS  
*date* - *results*

STUDIES  
*date* - *results*

ASSESSMENT / RECOMMENDATIONS  
The assessment and recommendations were formulated with Dr. ____.  
Outline the assessment/recommendations

A copy of this consultation was sent to the requesting physician, Dr. ____.

COPIES TO OTHERS  
**OUTPATIENT** -  
DON’T FORGET TO DICTATE A COPY TO THE MD WHO REQUESTED THE CONSULTATION  
--make sure to give the transcriptionists the address (not the fax as transcription won’t fax documents)

**INPATIENT** -  
DICTATE A COPY TO THE PATIENT’S PRIMARY PHYSICIANS  
--make sure to give the transcriptionists the address (not the fax as transcription won’t fax documents)
Percutaneous Needle Liver Biopsy
Anne Larson, MD

History
• First performed in 1883 by Paul Ehrlich (Germany) and further utilized in 1895 by Lucatello (Italy)
• First published series in 1907 by F. Schüpfer
• Achieved greater popularity in the 1930s --the second world war saw an increased use

Patient Selection - varies depending on article; generally:
• PT < 3 seconds prolonged; INR <1.5
• platelets > 80,000  (Dr. Carithers has requested that we use >100,000)
• no significant ascites

Techniques
• Intercostal
  - most frequent method used and rarely fails to obtain tissue
  - prelocalization by ultrasound useful  (Lindor, et al  Hepatology  1996;23:1079)
• Transvenous (transjugular)
  - uses a Tru-cut needle via jugular
  - liver fragments are usually smaller (sometimes compromising interpretation)
• Directed (Guided)
  - utilizes the Biopty™ gun
  - one hand to guide with ultrasound/the other uses the gun
  - liver fragments are usually smaller
• Fine-Needle Guided
  - smaller needle adds to safety but less satisfactory tissue samples obtained
  - may be useful for diagnosis of tumors (but also can compromise interpretation)

Types of Needles
• Menghini
• Klatson (the type used at the UW)
• Jamshidi (the type used at HMC)
• Tru-cut (modification of older Vim-Silverman needle)
• Biopty gun (biopeter)

Risks and Complications
• Overall Mortality - 0-0.33% (average ~0.01%)
• Pleurisy/Perihepatitis (Pain) - 25-50%
  - usually of little consequence (except makes the patient very uncomfortable)
  - CXR (if taken) may show a small pneumothorax
• Biliary Peritonitis - 0.04%  (0.009% mortality)
  - second most common complication
  - bile is usually from the gall bladder or a dilated duct
  - Tx: surgery frequently needed to seal the leak
• Hemorrhage - 0.13-1.7%
  - the most common complication (usually intraperitoneal, but may be intrathoracic)
  - severe hemothorax usually responds to blood transfusion and chest aspiration
  - risk factors (McGill  Gastro 1990 99:1396)
    - malignancy
    - age
    - female sex
    - number of needle passes
  - NOTE: hemorrhage is rare in the non-jaundiced patient
• **Intrahepatic Hematoma**  
  - ~2% @ 2-4 hours after biopsy / ~23% @ 24 hours (asymptomatic)  
  - can cause fever, ↑ ALT, ↑ Hct, RUQ pain

• **Hemobilia**  
  - follows a bleed from damaged vessel into a bile duct  
  - biliary colic can occur  
  - Dx: ultrasound or ERCP  
  - Tx: spontaneous recovery common (may need embolization)

• **Infection**  
  - transient bacteremia is common (esp. in patients with cholangitis) (Bubak Hepatol 1991 14:1063)  
  - septicemia is rarer (usually E. coli)

• **Hypotension (vasovagal)** - ~0.37-0.40%

• **Puncture of Other Organs** - ~0.21%

• **A-V Fistula**  
  - ~5.4% in one study when all patients looked at  
  - most close spontaneously (rarely require embolization)

• **Pleural Effusions** - <1%  
  - mechanisms:  
    - laceration of vasculature - hemothorax  
    - perforation of diaphragm - leakage of ascites  
    - biliary/pleural fistula (rare; <4 cases in world literature)

• **Pneumothorax** - <1%  
  - most are small and asymptomatic  
  - probably more common than
citations available upon request
Purpose of Study:
The multi-center ALF study group has the broad aims of 1) collect data concerning etiology, natural history and pathogenesis, and 2) studying new therapies for ALF. The main study is the prospective gathering of data regarding incidence, etiology, lab values, survival figures, and liver transplantation rates. Serum/tissue samples will also be collected. A 2nd substudy will evaluate the use of IV N-acetylcysteine (Mucomyst) vs. placebo (dextrose) in the treatment NON-ACETAMINOGEN PHEN ALF patients. Subjects have 10-15 cc’s of blood drawn daily for the first 7 days. One of our goals is to obtain blood from the first draw when the patient arrives (hopefully before they’ve received blood products or any therapy). Obviously, this can’t be done every time, but the closer to admission the first draw is done, the better. This necessitates calling the study team as soon as possible either before or after the patient arrives. Medical records will also be reviewed for demographic data (age, sex, race, etc), laboratory data, medical history, encephalopathy score, and physical exam findings unavailable to the investigator at enrollment. If liver biopsies are performed, we obtain a piece of this tissue as well.

INSTRUCTIONS:

1. Consent.
   a. ACETAMINOPHEN OVERDOSE AND WILSON’S DISEASE. Obtain consent (in folder labeled Consent Form 1) from the patient’s family members
      i. original signed consent to Anne Larson, MD
      ii. copy of signed consent in patient chart
      iii. copy of signed consent to patient and their family

   b. ALL OTHER FULMINANT PATIENTS. Obtain consents (in folder labeled Consent Form 1 AND folder labeled Consent Form 2) from the patient’s family members. They must sign both consent forms if they agree to both phases of the study. If they do not wish to participate in the randomized treatment trial, have them sign only Consent Form 1.
      i. original signed consent to Anne Larson, MD
      ii. copy of signed consent in patient chart
      iii. copy of signed consent to patient and their family

2. Blood Draws
   a. WEEKDAYS: Kim Chin (pager 540-3323) will help coordinate the blood draws. He will collect the blood from the nurses in the ICU and spin/aliquot/freeze it. He will also pick up all spun specimens from the hospital lab (from weekends and late night) and aliquot them.

   b. WEEKEND: use green clinical lab slip (in folder labeled Blood Collection Forms) to have blood drawn, spun, and held.

   c. NIGHTS: use green clinical lab slip (in folder labeled Blood Collection Forms) to have blood drawn, spun, and held.

3. Data Collection. Please fill in as much of the “Admission to Study” form as possible. Once you have enrolled the patient, Hao and I will take over the duties of following them through-out the study.

4. NAC/Placebo Administration. The order forms for the Study Drug are in the NAC Pharmacy Orders Folder. Randomization will be carried out by the pharmacy and they will send the drug/placebo to the ICU. The only side effect reported in previous studies was occasional wheezing (which responded to Benadryl and bronchodilators). No patients have had to be removed from drug.

THANK YOU FOR YOUR ASSISTANCE
Fulminant Hepatitis

**Etiology**

**Viral Hepatitis**
- Hepatitis B
- Hepatitis D along with B
- Other viral hepatitis (rare A, E, not C)

**Toxins**
- CCl₄
- mushrooms (amanita phalloides)
- yellow phosphorus

**Medications**
- INH
- Halothane
- Sulfa-containing drugs
- NSAIDs
- Acetaminophen
  (toxicity at lower doses seen in alcoholics
due to ↑ activity of enzyme P450-2E1)

**Cirrhosis** complicated by acute hepatitis

**The Decision Process**

The central issue to be clarified ASAP is whether the patient will be a transplant candidate. Being accepted in transfer to the UWMC does NOT mean that the decision has been made to transplant. In virtually every instance, the decision has been deferred until the patient is evaluated in our hospital. Often patients are not transplant candidates for a variety of reasons.

The Housestaff should page the hepatology service immediately upon the patient's arrival to the ICU. The hepatology fellow or attending will assess the patient and gather data regarding the patient's suitability for liver transplant. The fellow or attending will page the liver transplant coordinators if indicated. They will help initiate both the medical and social evaluation needed to reach a decision.

DO NOT mention anything about the possibility of a transplant to the patient or the family. Making the decision is frequently a difficult process in these acutely ill patients and there are often disagreements to be resolved. If asked, defer to the MICU attending, the Hepatology attending, or the Transplant Surgery Attending.

**Management**

**Access and Volume**

Put in a central line as soon as possible. Infuse crystalloid and albumin as needed to maintain a good urine output. These patients are often dehydrated, and ATN is often a more common cause of renal failure than the hepatorenal syndrome. Follow urinary sodium. Do not give free water the swelling brain.

Do not try to correct the prothrombin time or thrombocytopenia. FFP and/or platelet support should only be used in preparation for central access and/or bolting or if the patient is actively bleeding.

Do not put in subclavian or femoral lines in patients who will be going to the OR for transplant. Both cause problems in the OR when the patient is put on femoral-axillary bypass.

**Antibiotics**

Altering the anaerobic flora of the gut increases the risk of fungal infections when immunosuppression is given post-transplant. If needed, the best antibiotics are vancomycin and cefuroxime. Avoid using antibiotics that will alter the anaerobic flora if possible. If it is necessary to alter the gut flora, check with the transplant surgeons first. Data suggests that prophylactic antibiotics decreases the number of infections, but doesn't alter eventual outcomes.
Complications

Coagulopathy - DO NOT try to correct this
• marked elevation in prothrombin time seen (decreased production of factors 1,2,5,7,9, & 10)
  • this is one of the most sensitive indicators of “liver function” you have
  • PT mirrors prognosis and progress of disease
  • FFP and/or platelets only for procedures or active bleeding

Platelet Abnormalities
• <100,000 in ~70% of cases
• the count usually declines progressively over the course of the disease
• abnormal morphology and function seen (mechanism ??)
• increased risk of bleeding correlates with thrombocytopenia (not coagulopathy)

Hepatic Encephalopathy
• DO NOT GIVE SEDATIVES (if at all possible)
• Stage of encephalopathy is another one of the most sensitive “liver function tests” you have
• Depressed consciousness
  • leads to aspiration
  • intubate early (between stage 2 and 3 encephalopathy)

Again, try not to give sedatives in patients who are slipping into hepatic encephalopathy. The patients may go wild, however, and you will need to intubate and partially paralyze them to protect their airways and lines. Once patients reach stage 4 coma, there is no need to sedate them – they are calm and easy to manage. If sedation is necessary, we use the following medications:
• *Fentanyl* [100 μg (0.1 mg)] provides analgesia and sedation, and a dose-related depression of ventilation that lasts longer than analgesic effect. Because a single dose is cleared by redistribution, it can be used in the setting of liver failure with a rapid onset of action when given IV (immediate), a slower onset of ventilatory depression (5 min, but report up to 15 min), and a 30-60 minute duration of action. A single dose can easily be given to facilitate line placement. A drip may facilitate management of the patient, but daily “wake-ups” are mandatory to assess mental status.
• *Propofol* (0.5-1.5 μg/mL, continuous IV infusion) for sedation/anesthesia in patients with acute hepatic failure is very effective. The medication can cause hypotension without a change in heart rate. If patients are ventilated, cardiac output may fall some. Elimination is by hepatic conjugation (presumably by a system that is not affected by the hepatic failure) and renal excretion, but daily “wake-ups” are mandatory to assess mental status.

If the decision to transplant is made, an ICP monitor may be needed. An ICP monitor should be placed once intubation and sedation/paralysis are necessary. This monitor may buy 12-24 hours of brain protection while you await availability of a donor organ. The monitor helps to determine whether the patient will likely wake up after transplantation. There is great debate about whether to place an ICP monitor in patients who are not liver transplant candidates - we tend to manage these patients symptomatically.

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<thead>
<tr>
<th>Evaluation of Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IVA</td>
</tr>
<tr>
<td>IVB</td>
</tr>
</tbody>
</table>

Handbook -30
03/30/07
Hemodynamics
♦ decreased SVR with compensatory increased cardiac output
♦ Often can’t distinguish from sepsis (do not give prophylactic antibiotics)
♦ severity of abnormalities correlates with mortality

Cerebral Edema
♦ may occur in up to 80% of patients with fulminant hepatic failure
♦ May preclude liver transplantation (patients don’t wake up afterward)
♦ more commonly seen in patients with grade 3 or 4 encephalopathy
♦ Manifestations:
  ♦ increased muscle tone
  ♦ dilated pupils
  ♦ increased respiratory rate
  ♦ sudden increase in BP (or decrease in BP)
  ♦ loss of occulovestibular reflexes
♦ don’t do Doll’s Eyes maneuver (may increase CSF pressure)
♦ treatment
  ♦ place ICP monitor once intubation/sedation as needed
  ♦ maintain ICP <20 mmHg or CPP >30 mmHg (CPP = MAP – ICP)
  ♦ hyperventilate to pCO₂ <25 (acutely; longer term hyperventilation ineffective)
  ♦ mannitol 0.5 to 1.0 g/kg (to keep osm 310-320)
  ♦ pentobarbital coma (3-5 mg/kg IV)
  ♦ steroids are NOT effective

GI Bleeding
♦ needs endoscopy to determine the source of the blood
♦ Virtually always stress ulcers (unless in setting of acute on chronic liver disease)
♦ Prophylaxis should be given promptly (H₂ blockers or PPIs with monitoring of gastric pH)
♦ If bleeding is variceal
  ♦ Ask the endoscopists to avoid sclerosing the varices if at all possible – use variceal banding
    (ulcers from the sclerosis get infected with fungi in the postoperative state, and can bleed uncontrollably on the OR table during transplant). Sclerosis may preclude transplant
  ♦ Minnesota tube or TIPS can be used for intractable bleeding

Renal Failure
♦ seen in about 40-50% of cases of fulminant hepatic failure (70% of those with acetaminophen toxicity)
♦ Volume depletion (often see ATN and prerenal states)
♦ May need dialysis for volume, potassium, and acidemia. Institute dialysis early.
♦ Hepatorenal syndrome can also be seen (literature is mixed regarding this).

Hypoglycemia
♦ seen in up to 40% of cases (liver is main site of insulin metabolism)
♦ FHF leads to inappropriately high serum levels of insulin
♦ liver is also unable to metabolize glycogen or perform gluconeogenesis
♦ may need D₁₀ drip

Electrolyte imbalance
♦ decreased free water clearance seen → hyponatremia
♦ hypokalemia and hypophosphatemia due to renal losses

Acid-Base Disturbances
♦ primary respiratory alkalosis – in 50-60% of cases
accompanying metabolic alkalosis – in 25-50%
metabolic acidosis – very common
  • tissue hypoxia with lactic acidosis
  • inability of failing liver to metabolize lactic acid

Other
  • Multi-system organ failure
  • Hypoglycemia - may need D10 (a very poor prognostic sign)

Prognostic Features
Prothrombin Time
  • > 25 seconds (INR 3.85) good predictor of death
  • overestimates cell necrosis with acetaminophen OD (can get very high; cutoff is 7.7)

Coma (encephalopathy) - grade II 66% survival; grade III 42% survival; grade IV 18% survival

Etiology - survival without transplant
  • “Good”
    • acetaminophen - survival >70%
    • hepatitis A - survival >50%
  • “Bad”
    • hepatitis B - survival ~40%
    • drug-induced - survival ~10-15%
    • other viral - survival ~20%
    • Wilson's disease - survival 0%

King's College Criteria for Transplantation
  • Acetaminophen
    • pH <7.3 (irrespective of grade of encephalopathy)
    or all three of the following:
    • Grade III-IV encephalopathy
    • PT >35 seconds (INR >7.7)
    • Serum creatinine >3.4 mg/dL
  • Non-Acetaminophen
    • PT >35 seconds (INR >7.7) (irrespective of grade of encephalopathy
    or any three of the following:
    • Age <10 or >40 years
    • bad etiology
    • period of jaundice to development of encephalopathy >7 days
    • PT >25 seconds (INR >3.85)
    • serum bilirubin >17 mg/dL
APPROACH TO ABNORMAL LIVER TESTS

With few exceptions, most liver diseases can be accurately diagnosed by taking a meticulous history, recognizing the pattern of enzyme elevations, and rationally selecting a few "second-line" blood tests and imaging studies. When evaluating abnormal liver tests, the most important questions to address at the outset are:

1) Acute vs. Chronic (≥6 months; ??evidence of cirrhosis and/or portal hypertension)
2) Hepatocellular vs. Cholestatic
3) Asymptomatic vs. Symptomatic (fever, pain, impaired liver "function" tests = PT, Albumin, Bilirubin)
4) Recent insults to the liver: EtOH, medications, pregnancy, gallstones, viral hepatitis, herbs

HEPATOCELLULAR INJURY: predominantly ↑ AST & ALT +/- ↑ AP, GGT, Bili
- Severe (>1,000): ischemic, viral, or toxic hepatitis (e.g., acetaminophen)
- Moderate (2-10 x nl): EtOH (remember AST > ALT 2:1), chronic hepatitis, cirrhosis, neoplasm
- Mild (<3 x nl): fatty liver, EtOH, chronic hepatitis (particularly hepatitis C)

NOTE: ALT is fairly liver-specific, and two or more liver enzyme elevations ==> high likelihood of liver disease.

CHOLESTATIC LIVER DISEASE: predominantly AP +/- Bili
- GGT and 5'-nucleotidase are helpful to distinguish hepatobiliary source of alkaline phosphatase (AP) from extrahepatic sources (bone, small bowel, kidney, placenta, and leukocytes)
- Imaging (ultrasound +/- CT scan) is crucial to distinguish intra- vs. extrahepatic cholestasis

<table>
<thead>
<tr>
<th>Intrahepatic Cholestasis</th>
<th>Extrahepatic Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty liver (with diabetes &amp; obesity)</td>
<td>Biliary duct obstruction (ERCP is King!)</td>
</tr>
<tr>
<td>Tumors (primary - AFP, mets, lymphoma)</td>
<td>Benign - stones, strictures</td>
</tr>
<tr>
<td>PBC (females, (+) AMA in 95%)</td>
<td>Malignant - pancreatic; cholangioCA;</td>
</tr>
<tr>
<td>Hepatic cysts (U/S is diagnostic)</td>
<td>mets (breast, stomach, pancreas)</td>
</tr>
<tr>
<td>Hepatic granuloma (TB, syphilis, cocci)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>PSC (70% have UC; ERCP is diagnostic)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>AIDS Cholangiopathy (CD4 &lt;200; (+)</td>
</tr>
<tr>
<td>Drugs (estrogen, rifampin, chlorpromazine, TPN)</td>
<td>CMV and cryptococcus often seen</td>
</tr>
</tbody>
</table>

CHRONIC HEPATITIS: > 6 months of liver test abnormalities
Symptoms: fatigue, bleeding tendency, arthralgias, pruritis
Signs: spider angiomata, gynecomastia, evidence of portal hypertension
Etiology:
Common Causes: Account for 95% of cases and should guide the initial workup
- Hepatitis B - (+) HBsAg
- Hepatitis C - (+) HCV-Ab and PCR
- Hemochromatosis (fasting Fe/TIBC >50% and ↑ Ferritin
- Autoimmune Hepatitis (females, (+) AMA, (+) ASMA, ↑ globulins)
- Alcoholic liver disease

Rare Causes: should only be considered if above workup is negative
- Wilson's Disease (↓ ceruloplasmin)
- α1-Antitrypsin Deficiency (↓ α1AT level)
- Drugs (methotrexate, INH, amiodarone, methylodopa)
TRUE LIVER “FUNCTION” TESTS

PT - the most accurate prognostic factor in acute hepatitis and reflection of advanced nature of chronic hepatitis.

Albumin - half-life of 21 days, but subject to many non-hepatic influences as well

Bilirubin - distinguish unconjugated from conjugated and intra- vs. extrahepatic to narrow the dx
Herbal Preparations, Medicinal Plants and
Other Botanicals with Hepatotoxic Potential

Pyrrolizidine alkaloids (common names)
Amsinckia (tarweed; finger weed; fire weed; fiddle-necks)
Astragalus (Huang-Qi; beg kei, bei qi, hwanggi, astragali, tragacanth, membranous milk vetch)
Atractylis gummifera (white chameleon)
Azadirachta indica (Margosa; neem; Indian lilac; nimba)
Baccharis
Berberis vulgaris (berberry, pepperidge, jaundice berry, sow berry, mountain grape, Oregon grape)
Blighia sapida (ackee fruit; aki; akie)
Cacalia
Callillepsis laureola
Cassia angustifolia (senna, sennakot)
Crotalaria species (numerous products)
Cycas circinalis (cyasic)
Cynoglossum (hounds tongue; yao yong dao ti hu; tie gu san; beggar's lice; Chinese forget-me-not)
Echinacea
Erechtites
Erythroxylon coca (coca)
Eupatorium (gravel root; joe pye weed; feverwort; thoroughwort; boneset; aristolochia; snake root)
Hedeoma pulegoides and Mentha pulegium (Pennyroyal)
Heliotropium species
Larrea tridentata (chaparral, creosote bush, greasewood; gumis; chaparro)
Matte (Paraguay) tea
Piper methysticum (kava kava; ava-ava; yangona; keu; intoxicating pepper)
Sassafras albidum (ague tree; cinnamon wood; saxifrax; sassafrax)
Scutellaria lateriflora (Skull Cap; helmetflower; hoodwort; mad-dog weed; madweed; quaker bonnet)
Senecio species (ragwort; golden senecia; liferoot; squaw weed)
Symphytum officinale (comfrey)
Teucrium chamaedrys (germander)
Trachymene polium
Trichodesma
Valeriana officinalis (valerian; all-heal; amantilla; setwall; setewale; capon's tail; heliotrope; vandal root)
Viscum album (Mistletoe)
Werneria

Actual names of some of the Pyrrolizidine alkaloids:
  heliotrine, hydrophylline, intergerrine, jacobine, jacoline, jaconine, jacozine, lasiocarpine, monocrotaline,
  neoplatphylline, otosenine, platphylline, retrorsine, riddelline, senecionine, seneciphylline, senkirkine,
  spartloidine, yamataimine

Mushrooms
Aminita phalloides (Death Cap)
Lepiota helveola

Chinese herbal remedies and teas
Lycopodium serratum (Jin Bu Huan)  Ma-huang
Syo-saiko-to (Xiao-chai-hu-tang)       Gentianae (gentian root)
Dictamnus dasycarpus                   Bupleurum (hare's ear root)

NOTE: most Chinese medicines are adulterated with heavy metals and Western medicines
INSTRUCTIONS FOR ADMINISTERING THE NUMBER CONNECTION TEST

Fill out patient’s name, date, and other pertinent information on test sheet. Evaluate MENTAL STATE using following scale:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mental State</th>
<th>Asterixis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>No liver flap</td>
</tr>
<tr>
<td>1</td>
<td>Trivial change in behavior, short attention span</td>
<td>Rare liver flap</td>
</tr>
<tr>
<td>2</td>
<td>Obvious change in personality, disorientation for time</td>
<td>Frequent liver flap</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence, advanced confusion, semistupor</td>
<td>Continuous liver flap</td>
</tr>
<tr>
<td>4</td>
<td>Semicoma, coma</td>
<td>Unable to test for flap</td>
</tr>
</tbody>
</table>

Have patient sign name. The SIGNATURE is a crude index of mental state.

NOTE: each time you given the test, use the words of instruction specified below.

NUMBER CONNECTION TEST

PLACE DEMONSTRATION SAMPLE on table in front of patient and explain “Draw a line from circle 1 to circle 2 (demonstrate) and from circle 2 to 3 (demonstrate) from 3 to 4, and so forth. It’s OK to go through another circle or across another line. Draw the line as quickly as you can.”

THEN GIVE THE TEST. DEMONSTRATE STARTING POINT AND START TIMING. OBSERVE THE PATIENT DO THE TEST. If the patient makes a mistake, point it out immediately, e.g., “You skipped 4” (Point to it) Point to the last number correctly done and have the patient start from there. DO NOT STOP TIMING DURING CORRECTIONS.

When the patient has finished, record the elapsed time in seconds. If the patient cannot finish the test within 2 minutes, terminate the test at that time and record the last number completed correctly (e.g., 120 sec, 12). If the patient cannot do the test at all, record “can’t do”.

There are 4 different tests labeled I, II, III, and IV. They are equally difficult, and the time needed to complete each test is the same. Subsequent testing should be done by using the tests in sequence, to eliminate the learning factor.

ASSESSMENT

<table>
<thead>
<tr>
<th>Degree of Encephalopathy</th>
<th>Time in Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
</tr>
</tbody>
</table>
NUMBER CONNECTION TEST

PATIENT'S NAME____________________
DATE__________ TIME TO COMPLETE______ SECONDS
TESTER'S INITIALS__________ PT. CHART NO.______

PATIENT'S SIGNATURE ________________

BEGIN 1

24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5

END 25

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
1. Dial 186 to access system (or 685-0186) or Medquest 493-1200.

2. Enter the **ID CODE** given to you (5 digit; call 598-6175 if you do not have this number)

3. Enter the **REPORT TYPE** (2 digit; highlighted are the most commonly used):

<table>
<thead>
<tr>
<th>Report Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer summary</td>
<td>10</td>
<td>Initial Clinic Note</td>
</tr>
<tr>
<td>Interim summary</td>
<td>14</td>
<td>Telephone note</td>
</tr>
<tr>
<td>Emergency note</td>
<td>15</td>
<td>Consult (outpt) don’t use</td>
</tr>
<tr>
<td>NICU daily attg note</td>
<td>16</td>
<td>Consult (inpt)</td>
</tr>
<tr>
<td>NICU transfer sum</td>
<td>17</td>
<td>Operative report</td>
</tr>
<tr>
<td>NICU d/c summary</td>
<td>18</td>
<td>Surg. Neuromonitoring</td>
</tr>
<tr>
<td>Letter</td>
<td>20</td>
<td>Discharge summary</td>
</tr>
<tr>
<td>Attorney general narrative</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Clinic Note</td>
<td>30</td>
<td>Procedure Note</td>
</tr>
<tr>
<td>Letter</td>
<td>50</td>
<td>Discharge summary</td>
</tr>
<tr>
<td>Summary</td>
<td>60</td>
<td>Procedure Note</td>
</tr>
<tr>
<td>STAT</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

4. Enter the **SERVICE/CLINIC TYPE** (2 digit) - shown are the ones we use in hepatology

   58 - Hepatitis & Liver (outpt) - use for hepatology, tumor, and transplant clinics

5. Enter the **PATIENT NUMBER** (7-digit) for patient identification.

6. After ID entry is complete, you will hear a verbal prompt telling you to begin dictation followed by a soft “ready tone” assuring the system is ready for dictation. If you do not hear this tone, something has gone wrong and you may need to start over. **If you make a mistake, you can press the ‘**’ key and it will take you back a step for you to start again.**

7. The system is voice activated. The dictation will start and stop with the sound of your voice.

8. **IMPORTANT:** If you are ready to dictate more than one report, you do not have to call back in. When you have completed a report, touch the “5” on your telephone keypad and you will hear a verbal prompt instructing you to enter your 2-digit report type, 2-digit service type, and 7-digit ID number. Your 5-digit physician ID number will automatically be re-entered for you. After you enter your new report ID numbers, you will hear the verbal prompt asking you to continue with your dictation.

A number of liver diseases can result in progressive hepatocellular injury and cirrhosis. The most common of these are alcoholic liver disease, drug-induced liver injury, chronic hepatitis B and C, autoimmune liver diseases, and various metabolic disorders. Liver disease from many of these disorders can be prevented by timely intervention. If patients are diagnosed early in the course of disease, progressive liver cell injury can be arrested, resulting in normal liver function and life expectancy. For patients diagnosed late in the clinical course of disease, appropriate management of the complications of cirrhosis has become increasingly important because of the availability of liver transplantation.

ALCOHOLIC LIVER DISEASE

Approximately 25 - 40% of patients hospitalized in the United States have medical problems resulting from alcohol abuse. Excessive alcohol intake can result in a spectrum of liver injury ranging from fatty liver to cirrhosis. Fatty liver can occur even after moderate weekend drinking but usually resolves quickly with abstinence. Much more ominous is the development of necroinflammatory hepatocellular injury, commonly called alcoholic hepatitis. This pattern of injury appears to be an important step in the evolution of progressive liver injury and is a direct precursor of cirrhosis in many, if not all, patients. Alcoholic hepatitis and cirrhosis result in approximately 10,000 deaths annually in the United States.

CLINICAL FEATURES

Alcoholics typically underestimate their consumption or deny having a problem with alcohol. Several questionnaires have been developed to facilitate the diagnosis of alcoholism. The “CAGE” criteria, a battery of four questions referring to events occurring within a patient’s lifetime, continues to be commonly used, and is a practical means of screening for alcoholism. Most alcoholics have positive responses to at least two questions and approximately 50% respond positively to all four questions. In contrast, over 80 percent of nonalcoholic individuals have a negative response to all four questions and rarely do non-alcoholics have a positive response to more than two questions. A family history of alcoholism or a history of trauma should also raise a suspicion of alcohol abuse.

Symptomatic patients with alcoholic hepatitis and cirrhosis describe a variety of complaints including vague abdominal pain, anorexia, nausea and vomiting, weakness, diarrhea, weight loss, and fever. The most common physical finding is hepatomegaly. Other findings include hepatic tenderness, an audible bruit over the liver, jaundice, spider angioma, splenomegaly, ascites, edema, and, in more severe cases, varying degrees of hepatic encephalopathy. Temperatures as high as 104-105°F are seen in some patients. Prolonged fever lasting for weeks is not unusual. Surprisingly modest elevations of aminotransferase values are seen in patients with alcoholic hepatitis and cirrhosis, even when the disease is severe. AST levels are usually less than 300-500 IU and are associated with trivial elevation of ALT levels, resulting in an AST/ALT ratio > 3, which is characteristic of alcoholic liver disease. Alkaline phosphatase levels can vary from normal to values in the thousands. Bilirubin levels range from normal to 20-30 mg/dL and serum albumin may be normal or depressed to levels as low as 1.0-1.5 gm/dL. Most patients with alcoholic liver disease are anemic and have some degree of thrombocytopenia. In contrast, the white blood cell count is usually normal or elevated, occasionally to levels consistent with leukemoid states.

Although clinical features usually suffice for the diagnosis of alcoholic liver disease, liver biopsy is essential for precise determination of the severity of hepatic injury. Classic histologic features of alcoholic hepatitis include hepatocellular necrosis concentrated in pericentral areas, the presence of alcoholic hyaline (Mallory bodies) within damaged hepatocytes, and a surrounding infiltrate composed of polymorphonuclear leukocytes. Varying degrees of fatty infiltration are usually present. Fibrosis may be present, and many patients exhibit an unusual perisinusoidal distribution of fibrosis, at times with partial or complete obliteration of the terminal
hepatic venules, which may lead to portal hypertension. Cirrhosis can be identified by the presence of nodules of hepatic tissue completely surrounded by fibrous tissue.

PROGNOSIS AND TREATMENT
Because patients with alcoholic hepatitis and cirrhosis can experience a wide spectrum of liver injury, the prognosis can vary dramatically. Patients with severe disease have a very high mortality, approaching that of patients with fulminant hepatic failure. Clinical features suggesting severe disease include hepatic encephalopathy, marked prolongation of prothrombin time values, elevation of serum bilirubin above 25 mg/dl, depressed serum albumin, elevated serum creatinine, and older age. A simple formula called the discriminant function (DF) [(4.6 x prothrombin time) + serum bilirubin] has been shown to be quite useful in identifying patients with poor short-term survival. The prognosis of patients with alcoholic cirrhosis further depends on the number of complications experienced and whether they can abstain from further alcohol abuse.

Patients who can abstain from further alcohol intake have a surprisingly favorable prognosis. Individuals with alcoholic cirrhosis who have experienced no major complications have a five year survival rate of almost 90%; furthermore, patients who have previously experienced jaundice, ascites, or hematemia have a 60% chance of surviving five years. Even cirrhotics who have had jaundice, ascites, and evidence of poor synthetic function can completely recover clinically after discontinuing alcohol intake.

Corticosteroid therapy and treatment with pentoxifylline each have been shown to significantly improve short term survival in patients with severe alcoholic hepatitis manifested by hepatic encephalopathy or marked prolongation of prothrombin time and serum bilirubin values (DF > 90). No benefit has been shown in patients with milder disease. For patients with decompensated cirrhosis despite sustained abstinence, liver transplantation is the treatment of choice. Carefully selected patients have a remarkably good outcome, which equals or exceeds that of patients transplanted for other conditions.

DRUG-INDUCED LIVER INJURY
Patients who develop drug hepatotoxicity may have varied clinical presentations. Patients may have hepatocellular injury ranging from asymptomatic biochemical abnormalities to acute illness with jaundice that resembles viral hepatitis. Evidence of liver injury is most frequently seen four to six weeks after initiation of the offending drug. If injury is identified early and the drug is discontinued, complete recovery is the rule. However, if the drug is inadvertently continued, progressive hepatic damage can result in severe chronic liver injury or fulminant hepatic failure. Cholestatic reactions to therapeutic agents, characterized by marked elevation of alkaline phosphatase and jaundice, have a less ominous prognosis but can be quite prolonged and result in diagnostic confusion. Chronic drug-induced hepatotoxicity can result in a wide range of clinical and histologic features, which can resemble autoimmune hepatitis, fatty liver, granulomatous hepatitis, primary biliary cirrhosis, hepatic venoocclusive disease, or alcoholic hepatitis.

PATHOGENESIS
Two basic patterns of hepatic toxicity have been identified: (1) reproducible injury which occurs in every individual who ingests a sufficient quantity of the offending agent; and, 2) idiosyncratic reactions, which occur only in occasional individuals exposed to a particular drug and do not appear to be dose-dependent. The first type of injury, which can be reproduced in laboratory animals, often results from hepatic metabolism of an innocuous compound into an hepatotoxic metabolite. Liver injury may be enhanced by drug-drug interactions that increase concentration of the hepatotoxic metabolite. Classic examples of this type of injury include acetaminophen and carbon tetrachloride hepatotoxicity. However, most hepatotoxic drug reactions are idiosyncratic. The precise mechanism of hepatic injury in these cases can rarely be identified. Classical examples of idiosyncratic drug reactions include halothane, isoniazid, propylthiouracil, minocycline, and diclofenac. Because of their relative rarity, idiosyncratic reactions resulting in hepatic injury often escape detection during clinical trials of new therapeutic agents. The scope and severity of hepatotoxicity may
become apparent only after the drug has been approved and achieved widespread clinical usage. A classic recent example is the hepatotoxicity associated with troglitazone therapy.8

**ACETAMINOPHEN HEPATOTOXICITY**

The most common cause of severe drug-induced liver injury encountered in the United States is acetaminophen hepatotoxicity. Two clinical patterns of liver injury have been identified: (1) suicidal or accidental ingestion of large quantities of acetaminophen sufficient to cause hepatic injury; and, (2) ingestion of lesser quantities of drug in patients predisposed to injury by upregulation of hepatic enzymes that convert acetaminophen to a hepatotoxic metabolite.9

Acetaminophen is a common agent ingested by teenagers and young adults who wish to make a suicidal gesture or who are crying for attention because of problems with interpersonal relationships. Children also can accidentally ingest lethal quantities of acetaminophen. Over 95% of ingested acetaminophen undergoes hepatic metabolism to non-toxic metabolites via conjugation with sulfate or glutathione. Less than 5% of the parent compound undergoes intrahepatic metabolism by the cytochrome P450 IIE1 enzyme to a potentially toxic metabolite, which normally is converted to nontoxic byproducts by intrahepatic glutathione. Liver injury occurs only after exhaustion of hepatic glutathione stores and subsequent intrahepatic accumulation of the toxic metabolite. As a result, severe hepatotoxicity usually occurs only after ingestion of 12-15 grams of acetaminophen over a brief period of time. Patients seen within the first 12-24 hours usually have normal or near normal aminotransferase and serum bilirubin values. However, the severity of potential liver injury can be predicted by determining the serum acetaminophen level. Severe hepatotoxicity usually becomes manifest 48-72 hours after drug ingestion with marked elevation of AST and ALT values (often > 10,000 IU). In severe cases patients develop metabolic acidosis early in the clinical course and exhibit marked prolongation of prothrombin time values and hepatic encephalopathy. If the patient comes to clinical attention within the first 12-24 hours after acetaminophen ingestion, liver injury often can be prevented by administration of acetylcysteine, which acts as a surrogate for hepatic glutathione. Patients with severe hepatic injury should be referred to a center where liver transplantation is available. Fortunately, most patients with fulminant hepatic failure from acetaminophen hepatotoxicity completely recover with effective critical care management and rarely require transplantation.10

A less well recognized but potentially more serious form of acetaminophen hepatotoxicity occurs in individuals predisposed to injury by upregulation of the cytochrome IIE1 enzyme. These individuals can develop severe injury after ingestion of lower doses of acetaminophen than in the normal state. This type of drug toxicity is seen most commonly in chronic alcoholics who take excessive acetaminophen over a period of days to weeks for relief of a headache, toothache, or other minor pain.11 The clinical features noted in these patients are indistinguishable from alcoholic liver disease with one obvious exception – AST values are typically > 1000 IU, much higher those seen in patients with even the most severe alcoholic liver disease. Because the liver injury has already occurred in these patients by the time of hospitalization, acetaminophen levels are not helpful for diagnosis or management. Recognition of the cause of the unusually elevated aminotransferase levels comes from careful questioning of the patient and family about acetaminophen ingestion in the days to weeks prior to hospitalization. The morbidity and mortality associated with this condition are quite high.12 Furthermore, because many of these patients have a history of recent heavy alcohol use, few are candidates for liver transplantation. Isoniazid is another commonly used agent which can upregulate the IIE1 enzyme and predispose patients to acetaminophen hepatotoxicity.13

**OTHER HEPATOTOXIC AGENTS**

Other frequently used agents which can cause acute hepatocellular include sulindac, diclofenac, dantrolene, propylthiouracil, various sulfonamides, and ketoconazole. In a number of cases patients have developed fatal fulminant hepatic failure. Chronic liver injury can be seen with dantrolene, isoniazid, methyldopa, nitrofurantoin, and sulfonamides. A number of antiretroviral agents exhibit significant hepatotoxicity, even those use for prophylaxis after occupational exposure.14,15 Herbal preparations, such as the Chinese herbal tea...
Jin Bu Huan and Ma-Huang, germander, and chapperal also can cause severe liver injury.\textsuperscript{16,17} The use of dietary supplements and other alternative medications also may result in significant liver injury.\textsuperscript{18,19}

The timing and clinical features of drug reactions often help in their recognition and management. Isoniazid is a good example. Three to four weeks after initiation of therapy, 10-15\% of patients develop mild aminotransferase elevations that resolve despite continuation of the drug. In contrast, liver injury occurring after six months of therapy is severe and may not be reflected by the patient’s symptoms. Therefore, elevated aminotransferases noted after six months of treatment should be followed carefully and the drug should be discontinued if there is a persistent rise in AST and ALT values or any evidence of synthetic dysfunction. Combined use of isoniazid and rifampin appears to enhance the risk of hepatotoxicity. The combination of rifampin plus pyrazinamide also appears to be particularly hepatotoxic.\textsuperscript{20}

Phenytoin hepatotoxicity is seen most frequently after 4-6 weeks of treatment and is associated with fever, diffuse lymphadenopathy, maculopapular rash, splenomegaly, leukocytosis, and atypical lymphocytosis suggesting infectious mononucleosis or lymphoma. Continuation of therapy despite these symptoms can result in fulminant hepatic failure.

Allopurinol therapy occasionally results in a systemic vasculitis manifested by fever, rash, eosinophilia, hepatitis and renal failure. These reactions occur most frequently in patients with mild azotemia in whom the dose of allopurinol is not adjusted for the degree of renal insufficiency.

Minocycline, frequently used for control of acne, can cause chronic hepatitis with positive antinuclear antibodies, which can be difficult to distinguish from autoimmune hepatitis.\textsuperscript{21}

More than 50 drugs have been associated with granuloma formation in the liver. Common offenders include allopurinol, chlorpromazine, dapsone, diltiazem, metolazone, oxacillin, phenylbutazone, phenytoin, procainamide, quindine, a variety of sulfa drugs, and tolbutamide.

Although less serious than hepatocellular drug injury, drug-induced cholestasis can result in considerable diagnostic confusion. The agents most commonly associated with cholestatic reactions include chlorpromazine and other phenothiazines, gold, chlorpropamide, oral contraceptives, androgens, tolbutamide, and erythromycin. A number of recent reports have identified the combination of amoxicillin-clavulenic acid as a common cause of cholestatic hepatotoxicity.\textsuperscript{22} Although resolution may be slow, complete recovery after discontinuation of the offending agent occurs in most cases of drug-induced cholestasis.

CHRONIC VIRAL HEPATITIS

Five distinct hepatitis virus (A-E) have been described. Hepatitis A and E typically are acquired from ingestion of food or water contaminated with the virus or from close household contact with an infected individual. Although most infections are asymptomatic, occasional patients develop severe disease, including fulminant hepatic failure. However, chronic infection does not occur with either of these viruses. Hepatitis D virus infection, typically acquired from injection drug use, requires the presence of hepatitis B infection for its replication. Although common in southern Europe and South America, this infection is extremely uncommon in the United States. Hepatitis B and C have emerged as the most important forms of viral hepatitis, primarily because of the risk of chronic infection and long-term sequelae of cirrhosis and hepatocellular carcinoma.

HEPATITIS B

It is estimated that 300-350 million individuals worldwide have chronic hepatitis B, including almost 1 million Americans. In many Asian countries 5-10\% of the population have chronic hepatitis B infection. The risk of developing chronic hepatitis B infection is highly dependent on the age at which infection occurs. Almost 90\% of neonates who acquire HBV at birth from maternal-fetal transmission develop chronic infection. In addition, roughly half of children who are infected within the first 5 years of life from household exposure develop
chronic infection. These individuals have an extraordinary risk for progression to cirrhosis and hepatocellular carcinoma later in life. In contrast, the risk of acquiring hepatitis B from adult infection is only 3-5%. Patterns of infection vary widely among different geographic locales. In most of Asia and Africa hepatitis B is acquired early in life from maternal-fetal transmission or household contact. Among Native Americans in Alaska infection occurs most frequently in early childhood from household contact with the virus. In contrast, in most other regions in the United States, acute hepatitis B is most commonly seen among young adults who acquire the infection from injection drug use or sexual contact with an infected individual. Nevertheless, an estimated 20,000 cases of maternal-fetal transmission of hepatitis B occur in the United States each year.

Remarkably safe and effective vaccines are available for the prevention of hepatitis B infection. In addition, high-titer preparations of antibody against hepatitis B (HBIG) are available for short term post-exposure prophylaxis. Vaccination against hepatitis B appears to offer lifetime protection against infection. As a result, uniform vaccination of all children is now recommended. Studies suggest that childhood vaccination can prevent the long-term complications of chronic hepatitis B infection, such as hepatocellular carcinoma. Because of the high risk of chronic infection following maternal-fetal transmission of hepatitis B, all women should be screened for the presence of hepatitis B infection. Infants born to HBsAg-positive mothers should receive immediate inoculation with HBIG followed by vaccination for hepatitis B. These measures prevent over 90% of maternal-fetal transmission of the virus.

For patients with chronic hepatitis B virus infection, two forms of therapy are available. Alpha interferon (5M units daily for 16 weeks) is effective in eradicating viral replication in approximately 40% of patients. Furthermore, patients who respond to treatment with loss of HBeAg and disappearance of circulating viral DNA often become HBsAg negative within 5-6 years. Since interferon administration frequently results in transient exacerbation of disease activity, it should be used only in patients with good hepatic function. Furthermore, it is not useful in immunosuppressed patients. Side effects include malaise, flu-like symptoms, and depression. Because leukopenia and thrombocytopenia can occur, blood counts should be followed during therapy. A number of nucleoside analogues have been used for treatment of patients with chronic hepatitis B. Of these, only lamivudine has been FDA approved. It appears to have equal efficacy compared to alpha interferon. Since lamivudine is an oral medication with few side effects, it is much better tolerated than interferon therapy. Neither the optimum duration of treatment and long-term outcome of therapy are known. In addition, there is concern about mutations of the virus with long-term therapy and the development of resistance. Both interferon and lamivudine are most effective in patients with elevated aminotransferases and relatively low levels of circulating virus. Unfortunately, many Asian HBV carriers have normal aminotransferases and relatively high levels of HBV DNA; as a result, few respond to current modes of therapy. Because lamivudine does not exacerbate liver injury, it is particularly useful in patients with decompensated cirrhosis. It also is effective in immunosuppressed patients. Liver transplantation can be very effective in patients with end-stage liver disease secondary to chronic hepatitis B. However, special precautions are necessary to prevent serious, life-threatening HBV recurrence following the operation. Continuous HBIG treatment and lamivudine therapy are both useful in this setting.

HEPATITIS C

It is estimated that 3.9 million Americans have chronic hepatitis C and that 25,000 new cases occur annually. Patients infected with hepatitis C have a 50-85% chance of developing persistent viral infection and a 70% probability of chronic liver disease. The primary risk factors for acquisition of hepatitis C include blood transfusions before 1992 and injection drug use. Maternal-fetal transmission occurs in approximately 10% of cases but most infants infected at birth appear to have mild liver injury and often clear the virus spontaneously. Although sexual transmission of hepatitis C may occur, it appears to be very inefficient. In particular, there is an extremely low risk of sexual transmission between individuals in long-term monogamous relationships. Current ELISA assays are both sensitive and specific for anti-HCV. Confirmation of active infection is achieved by detecting circulating HCV RNA. Both the level of circulating virus and genotype of HCV infection are important determinants of response to antiviral therapy but appear to have no influence on the prognosis of disease. Patients with chronic hepatitis C can have insidious progression to cirrhosis and high

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risk for hepatocellular carcinoma; however, many patients have minimal, if any, liver disease after years of chronic infection.\textsuperscript{38} Men, individuals infected after the age of 40, and those who abuse alcohol have more rapid progression of liver disease.\textsuperscript{39} Hepatitis C infection also can result in a variety of extrahepatic manifestations including mixed cryoglobulinemia, glomerulonephritis, and porphyria cutanea tarda.\textsuperscript{40} It is estimated that 5-10,000 patients die each year in the U.S. from end stage liver disease due to chronic hepatitis C. As a result, cirrhosis due to chronic hepatitis C has become the leading indication for liver transplantation in the U.S. At present, there is no reliable means of preventing HCV infection other than avoiding high-risk exposure. However, approximately 50\% of patients with chronic hepatitis C treated with the combination of pegylated interferon and ribavirin achieve sustained clearance of the virus after completion of therapy.\textsuperscript{41}

AUTOIMMUNE DISORDERS
Both the liver and bile ducts can be affected by autoimmune disorders. Three distinctive clinical syndromes have been characterized, each with a different anatomical target of injury: the hepatocyte in autoimmune hepatitis, small intralobular bile ducts in primary biliary cirrhosis, and larger bile ducts in primary sclerosing cholangitis.

AUTOIMMUNE HEPATITIS
Classic autoimmune hepatitis (type I) is most commonly seen in young and postmenopausal women. Young women often present with cessation of menses and have fatigue and lethargy as prominent symptoms. Spider angiomata, palmar erythema and splenomegaly are common physical findings. Most patients have positive antinuclear and anti-smooth muscle antibodies and diffuse hyperglobulinemia on serum protein electrophoresis.\textsuperscript{42} A second form of autoimmune hepatitis seen primarily in Europe (type II) is characterized by the presence of anti-liver kidney microsomal antibodies and appears to progress to cirrhosis more frequently.\textsuperscript{43} Patients with progressive chronic hepatitis manifested by histologic features of bridging fibrosis, submassive necrosis, or active cirrhosis have a poor prognosis. In these patients corticosteroid therapy can result in marked improvement in survival. Most patients respond dramatically to treatment with resolution of symptoms, normalization of aminotransferase values and improvement in synthetic function within two to three months.\textsuperscript{44} However, because of the high complication rate of chronic corticosteroid therapy, especially in patients who receive more than 20 mg daily for extended periods, only patients with severe disease should be treated. Azathioprine can be useful both as an adjunct to corticosteroids in inducing remission as well as for long term maintenance.\textsuperscript{45} Patients who cannot tolerate either corticosteroids or azathioprine often respond well to cyclosporine therapy. In patients who fail to show an initial response to immunosuppressive therapy or in those who have insidious progression to portal hypertension despite biochemical resolution of disease, liver transplantation is quite effective.

PRIMARY BILIARY CIRRHOSIS
Primary biliary cirrhosis is a cholestatic disorder which occurs most commonly in middle-aged women.\textsuperscript{46} Patients frequently complain of pruritus and have marked elevation of alkaline phosphatase levels. Associated biochemical features include elevated IgM levels and positive antimitochondrial antibodies. Radiographic studies of the biliary tree reveal no evidence of extrahepatic biliary obstruction. Liver biopsy typically shows inflammation around small bile ducts with nonsuppurative cholangitis. With progressive disease there is increasing fibrosis and progression to cirrhosis.\textsuperscript{47}

Common symptoms include fatigue and pruritus. Most patients have hepatomegaly; some have splenomegaly, xanthomata, xanthelasma and hyperpigmentation. Many patients have associated autoimmune features, particularly Sjögren’s syndrome, autoimmune thyroiditis, and renal tubular acidosis. Severe pruritus can be a significant clinical problem and these patients are at risk for malabsorption of fat soluble vitamins and zinc. Vitamin A and zinc deficiency can result in disturbances in night vision and vitamin E malabsorption, although much less common, can cause a neurologic syndrome characterized by ataxia, ophthalmoplegia, arreflexia, proprioceptive impairment, and paresthesias. However, the most significant clinical problem for patients with
PBC is bone disease characterized by impaired osteoblastic activity and accelerated osteoclastic activity. Calcium and vitamin D should be carefully monitored and appropriate replacement instituted. In addition, vigorous physical activity should be encouraged. Because of the potential for bone disease, corticosteroids can be particularly deleterious in patients with PBC.

Most patients remain asymptomatic for years. However, with time most show a decline in survival when compared to the general population. The preterminal phase is heralded by jaundice. Four large controlled trials of ursodeoxycholic acid have demonstrated dramatic improvement in liver function tests and a trend toward improved survival. Although many patients ultimately require liver transplantation, their outcome following the operation is the best seen with any liver disease.

PRIMARY SCLEROSING CHOLANGITIS

Sclerosing cholangitis is characterized by inflammation and fibrosis of the biliary tree. Involvement can include the extrahepatic bile ducts, the intrahepatic ducts, or both. Young men are most frequently affected. There is a strong association with ulcerative colitis. Symptoms include fatigue, pruritus, jaundice, abdominal pain, and recurrent fever due to repeated episodes of bacterial cholangitis. Hepatosplenomegaly and jaundice are the major physical findings. Biochemical findings reflect the chronic cholestatic nature of the disease with marked elevations in alkaline phosphatase, intermittent elevations in bilirubin, and minimal increases in aminotransferase values. The diagnosis is confirmed by endoscopic cholangiography which reveals multifocal areas of stricture and dilatation giving a beaded appearance to the involved portions of the extrahepatic and intrahepatic biliary tree. Attempts to surgically bypass obstructed areas are doomed to failure and are contraindicated because they significantly increase the risk of liver transplantation, which at present represents the only definitive form of therapy.

The clinical course of patients with sclerosing cholangitis is quite variable. Although many patients remain asymptomatic for long periods, nearly 60% ultimately become symptomatic and 25% develop liver failure leading to death or the need for liver transplantation. Patients with sclerosing cholangitis also are at high risk for developing cholangiocarcinoma and those with PSC and ulcerative colitis are strongly predisposed to colon cancer.

METABOLIC DISEASES

A variety of metabolic diseases can cause chronic hepatitis. The most common are Wilson disease, alpha-l-antitrypsin deficiency, and hemochromatosis.

WILSON DISEASE

Wilson disease is an autosomal recessive disorder manifested by deficient biliary copper elimination with a prevalence of 1 in 30,000. The Wilson disease gene has been cloned and localized to chromosome 13. However, there are so many genetic alterations associated with Wilson disease that genetic screening with probably never be feasible. Patients with Wilson disease gradually accumulate copper in the liver during the first two to three decades of life. At some point, usually between ages 15 and 25, the copper is redistributed causing liver injury, often associated with hemolysis and renal tubular defects. Patients can present with acute or fulminant hepatitis; however, a more common presentation is that of chronic hepatitis. There may be mild neurologic dysfunction with loss of concentration or emotional outbursts that may lead to psychiatric intervention. If left untreated, patients ultimately develop irreversible neurologic damage and permanent disability; however, with early treatment, long term survival is seen in over 90% of patients. Both the hepatic and neurologic sequelae can be prevented by administration of 1-2 g of penicillamine daily. Patients who develop severe toxic reactions to penicillamine can be treated effectively with trientine. Oral zinc therapy may also be effective, particularly in patients with neurological disease. The diagnosis of Wilson disease should be considered in any patient with chronic hepatitis under 50 years of age. Clinical diagnosis is based on depressed
ceruloplasmin levels (<20 mg/dl), increased urinary copper excretion (>100 μg/day), the presence of Kayser-Fleischer rings, and detection of abnormally high hepatic copper levels (>250 μg/g).

**ALPHA-1-ANTITRYPSIN DEFICIENCY**

Homozygous PIZZ alpha-1-antitrypsin (A1AT) deficiency affects between 1 in 600 to 1 in 7,000 infants and is the most common genetic cause of liver disease in children. In addition, there is an increased risk of cirrhosis and hepatocellular carcinoma in older patients. It is intriguing, however, that only 15% of patients with A1AT deficiency develop clinical manifestations. It has been postulated that other cofactors are necessary for disease to develop. The most common clinical presentations of alpha-1-antitrypsin deficiency include: (1) chronic obstructive pulmonary disease affecting primarily the lower lobes; (2) cholestatic jaundice in infants often progressing to cirrhosis by the age of ten; and (3) chronic hepatitis and cirrhosis in adults. Depressed serum alpha-1-antitrypsin levels and demonstration of sequestered alpha-1-antitrypsin granules within hepatocytes on liver biopsy establish the diagnosis. There is no effective medical therapy for the hepatic complications alpha-1-antitrypsin deficiency; however, liver transplantation is curative.

**HEMOCHROMATOSIS**

Hemochromatosis is the most common genetic disorder causing liver failure, particularly among individuals of Northern European descent. In patients with well characterized hereditary hemochromatosis, 85-90% are homozygous for a single missense mutation in the gene (HFE), which is located on the short arm of chromosome 6. This mutation, which results in a substitution of tyrosine for cysteine at amino acid 282, is referred to as the C282Y mutation. This appears to ultimately result in abnormal intestinal iron absorption and slowly progressive accumulation of iron in the liver, pancreas, heart and brain. It is estimated that 0.5% of the U.S. white population may be homozygous for the C282Y mutation. Patients with hemochromatosis commonly present in their fifties and sixties with hepatomegaly and chronic hepatitis. If the disease is not recognized, progression to diabetes, cardiomyopathy and pituitary failure can occur. Hemochromatosis should be suspected in any patient with transferrin saturation > 45%. Elevated serum ferritin levels are associated with tissue damage from iron. However, younger patients with hemochromatosis may not have elevated ferritin values. For this reason, measurement of transferrin saturation is a better screening strategy.

On occasion, it can be quite difficult to distinguish patients with alcoholic liver disease and secondary iron overload from those with end stage liver disease secondary to idiopathic hemochromatosis. Both conditions are common. Overlapping clinical features include hepatomegaly, glucose intolerance, testicular atrophy, and cardiomyopathy. In hemochromatosis, testicular atrophy is usually due to excessive pituitary accumulation of iron with secondary gonadal failure, whereas in alcoholics testicular failure results from toxic effects of alcohol on the testes. FSH and LH levels can be useful in distinguishing these two causes of testicular failure. Diabetes is a classic feature of idiopathic hemochromatosis; however, 80% of alcoholic cirrhotics have impaired glucose tolerance because of decreased peripheral sensitivity to insulin. In addition, alcoholics often have increased serum iron values and increased transferrin saturation. Serum ferritin also is frequently increased among patients with alcoholic hepatitis and cirrhosis.

The best methods of differentiating hemochromatosis from alcoholic liver disease with iron overload are quantitative determination of hepatic iron stores and genetic tests for hemochromatosis. Patients with liver disease secondary to hemochromatosis typically have hepatic iron levels greater than 1000 μg per 100 ml dry weight of tissue. Although patients with alcoholic hepatitis and cirrhosis have higher hepatic iron concentrations than normal, values rarely exceed 500 μg per 100 ml and are never higher than 1000 μg per 100 ml. The greatest difficulty comes in separating patients with alcoholic cirrhosis from young patients with asymptomatic idiopathic hemochromatosis. This can be accomplished by dividing the hepatic iron content by the patient’s age, creating an hepatic iron index (Hepatic iron index = Hepatic iron/ patient age). Patients with homozygous hereditary hemochromatosis have values > 2.0 whereas alcoholics with iron overload usually have values < 1.5 μg/g dry weight/age in years. Genetic tests for hereditary hemochromatosis also help to eliminate many of these diagnostic challenges.
If hemochromatosis can be detected prior to the development of cirrhosis, all of its manifestations can be prevented by vigorous and regular phlebotomy. However, once cirrhosis develops, patients remain at high risk for hepatocellular carcinoma despite successful phlebotomy.

**COMPLICATIONS OF CIRRHOSIS**

Gastrointestinal hemorrhage, hepatic encephalopathy, ascites, renal failure, and life-threatening infections are major complications of cirrhosis which general internists are required to manage.

**GASTROINTESTINAL HEMORRHAGE**

Hemorrhage from duodenal or gastric ulcers, Mallory-Wei ss tears, portal gastropathy, and esophageal varices are common among patients with cirrhosis. Because bleeding often is from a source other than varices and since the management of variceal bleeding differs so dramatically from that employed for other causes of hemorrhage, early identification of the bleeding site by endoscopy is essential.

Mortality from variceal hemorrhage averages 30%. Furthermore, patients have a high risk of rebleeding after the initial event. Therefore, early identification of the presence of varices is important. Over a third of patients with splenomegaly and thrombocytopenia have large esophageal varices. A variety of treatment options are now available for preventing and treating variceal bleeding including pharmacologic agents, sclerotherapy, variceal banding, portocaval shunts, transjugular intrahepatic portosystemic shunts (TIPS), and liver transplantation. The timely and appropriate use of these various therapeutic modalities have become essential to the optimum management of patients with portal hypertension and esophageal varices.

**Pharmacologic Agents**

In patients with large esophageal varices which have not bled, treatment with nonselective beta blockers both reduces the risk of bleeding and improves survival. The goal of treatment with propanolol or nadolol is to reduce the resting pulse by 25%. The most commonly used splanchnic vasoconstrictors for active variceal bleeding are vasopressin plus nitrates, somatostatin, and octreotide. Octreotide has become popular primarily because of its ease of use and availability.

**Endoscopic Therapy**

Endoscopic sclerotherapy is effective in controlling acute variceal bleeding in 75-90% of patients and is more effective than pharmacologic agents alone. Serious complications are seen in 10-30% of patients. Minor complications include fever, retrosternal chest pain, and transient dysphagia. Major complications include deep esophageal ulcerations with bleeding, mediastinitis, pleural effusions, esophageal strictures, bronchial-esophageal fistulae, ARDS, pneumothorax, and portal venous thrombosis. Variceal ligation is performed using a modified endoscope equipped with a preloaded elastic rubber band. Suction is used to draw the variceal mucosa into a cylinder affixed to the tip of the endoscope; a trip wire is used to release a rubber band around the base of the suctioned varix. The variceal tissue eventually sloughs leaving a shallow superficial ulcer. Variceal ligation compares favorably with sclerotherapy for treatment of bleeding esophageal varices. Control of active bleeding is equally effective; however, complications are less frequent and fewer treatment sessions are required for eradication with band ligation. It is currently controversial whether repeated band ligation or continued use of nonselective beta blockers is the most effective means of preventing recurrent bleeding from esophageal varices.

**Portosystemic Shunts**

The transjugular intrahepatic portosystemic shunt (TIPS) provides a non-operative approach to variceal bleeding in patients who have failed sclerotherapy or banding. A transjugular approach is used to manipulate a guide wire through the superior vena cava, right atrium, and inferior vena cava into the hepatic veins using fluoroscopic guidance. A needle is used to advance the wire through the liver parenchyma into the right portal vein. An angioplasty balloon then is used to dilate a tract between the hepatic and portal veins, allowing
placement of a self expanding metallic stent. In experienced hands the procedure can be performed in two to three hours. Complications include hepatic capsule perforation, intraabdominal bleeding, stent migration or occlusion, hemobilia, AV-fistulae, deterioration of liver function, and hepatic encephalopathy. Although the long-term benefits of TIPS remain to be demonstrated, it is a practical option for patients who have failed standard techniques to stem variceal hemorrhage and in patients with bleeding gastric varices. It also provides an effective bridge to liver transplantation in patients with recurrent variceal hemorrhage. The risk of a TIPS procedure can be calculated using a simple clinical model.

Surgical portal systemic shunts are effective in controlling variceal hemorrhage; however, they have never been shown to increase survival in patients with cirrhosis. Such shunts are being used less and less frequently because of the high operative risk in patients with severe liver disease. However, in patients with well compensated cirrhosis who have intractable variceal bleeding, distal splenorenal or mesocaval shunts are reasonable options.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a diffuse disturbance in cerebral function commonly seen in patients with decompensated cirrhosis. Alterations in cerebral function range from subtle disturbances in thought processes to deep coma. The pathogenesis of the condition remains controversial; nevertheless, effective treatment is available.

Pathogenesis

Encephalopathy associated with severe liver disease is thought to be caused by inadequate hepatic degradation of metabolic toxins that, when present in high enough concentrations, interfere with the cellular function of the brain. Impaired degradation of these toxins presumably occurs either because the mass of functioning hepatocytes is too small or because uptake of toxins into hepatocytes is compromised by shunting of blood around or through the liver. Potential toxins include ammonia, methionine, and fatty acids. Reversible hepatic encephalopathy can be produced experimentally by oral administration of any of these compounds to patients with cirrhosis. If antibiotics are given before administration, no alteration in mental status is seen, suggesting that metabolites produced by intestinal bacteria, rather than the parent compounds, are responsible for the encephalopathy. There is evidence for a synergistic action between mercaptans and ammonia and between fatty acids and ammonia. Although the pathogenesis of hepatic encephalopathy is clearly more complex than simple accumulation of ammonia, therapeutic maneuvers that decrease ammonia levels are effective in preventing and treating the disorder.

The intestine and the kidney are the major sites of ammonia production. In the intestine blood and dietary protein are the major substrates for ammonia production. Ammonia produced in the renal tubular cell can combine either with hydrogen to form ammonium ions and facilitate acid excretion, or may be released into the renal vein. When carbonic anhydrase inhibitors are used, ammonia concentration in the renal veins increases, adding an additional source of ammonia to the blood.

The liver contains unique urea cycle enzymes that convert ammonia into urea. Reduced capacity for urea synthesis, plus shunting of portal blood around and through the liver, combines to diminish urea production and cause systemic accumulation of ammonia.

The concentration of ammonia is always higher in the brain than in the blood. Since the brain is devoid of a urea cycle, intracerebral ammonia is converted exclusively to glutamine. Rapid accumulation of glutamine can result in osmotic attraction of water, cell swelling, and cerebral edema.

Other proposed mechanisms for depressed cortical function in patients with hepatic encephalopathy include accumulation of "false neurotransmitters" due to absorption of biogenic amines from the gut, excessive activity of central nervous system gamma-aminobutyric (GABA) activity, and accumulation of benzodiazepine-
like compounds in the blood and brain. However, more evidence is needed before the importance of these hypotheses in the pathogenesis of hepatic encephalopathy can be determined.

**Diagnosis**

The diagnosis of hepatic encephalopathy must be based on appropriate history and physical findings. No laboratory tests are sensitive or specific for hepatic encephalopathy. The ammonia level is elevated in most, but not all, patients and may be useful in following the course of an individual patient. If ordered, a fasting arterial sample should be obtained, placed on ice, and tested by a laboratory experienced in its measurement. Cerebrospinal fluid glutamine levels are elevated in most patients with hepatic encephalopathy. The EEG is helpful in staging the degree of encephalopathy; however, the changes seen are not specific for hepatic encephalopathy.

**Treatment**

There are two goals of therapy in patients susceptible to hepatic encephalopathy: to decrease accumulation of ammonia and other toxins in the circulation and brain; and to avoid any medications which may independently alter cerebral function. Increased ammonia absorption from the intestine can result from dietary indiscretion, GI bleeding, constipation or uremia. Excessive dietary protein should be avoided. Gastrointestinal bleeding must be controlled and the gut cleansed with purgatives. Constipation should be prevented and good renal function should be maintained to prevent urea accumulation.

The amount of ammonia and other toxins absorbed from the gut can be decreased by lactulose, a non digestible disaccharide which is metabolized by the intestinal flora into a variety of small organic acids. Acidification of the colon results in catharsis, diminished bacterial production of ammonia, and trapping of ammonia within the gut because of lowered colonic pH. Oral neomycin also is effective in diminishing ammonia absorption from the intestine by interfering with the conversion of urea to ammonia by colonic bacteria. Vancomycin and metronidazole can be used in resistant cases.

**ASCITES**

The treatment of ascites has undergone radical revision over the past few years. Cautious diuresis has been replaced by vigorous paracentesis. The remarkable safety and efficacy of large volume paracentesis also has led to a reexamination of the pathogenesis of ascites.

**Pathogenesis**

Ascites presumably develops because of perturbation of Starling forces throughout the hepatic sinusoids and splanchnic capillary bed. The hepatic sinusoids have a discontinuous membrane which permits free egress of plasma proteins. As a consequence, there is minimal oncotic pressure to oppose any increase in hydrostatic pressure within this large vascular bed. Any increase in sinusoidal pressure results in a massive outpouring of lymph into the abdominal cavity. When the capacity of the lymphatics to drain the abdomen is overwhelmed, ascites develops.

Significant ascites would not accumulate were it not for avid renal sodium retention; however, the factors which initiate this process remain highly controversial. The classical "underfill" theory presumes that formation of ascites depletes intravascular volume and results in sodium retention by the kidney as a normal compensatory mechanism. However, most investigators have found increased, rather than decreased, plasma volume in patients with cirrhosis and ascites. Furthermore, in dogs with chemically induced cirrhosis, avid renal sodium retention occurs before ascites accumulates. These observations support the "overflow" theory of ascites formation, which proposes that sodium retention is the primary event in initiating ascites formation with subsequent expansion of the intravascular volume and intraabdominal fluid accumulation.

A third hypothesis proposes that peripheral arterial dilatation, triggered initially by splanchnic vasodilatation, leads to renal sodium retention and ascites formation as a response to arterial underfilling.
Diagnostic Evaluation
The vast majority of patients with ascites have cirrhosis. However, in a significant minority of patients ascites is a manifestation of another disease process. These nonhepatic causes of ascites such as tuberculosis or chlamydia peritonitis, myxedema, or constrictive pericarditis may be curable but require specific therapy. The best means of differentiating cirrhotic from noncirrhotic ascites is the serum-ascites albumin gradient which involves subtracting the ascitic fluid albumin value from the serum albumin value. Patients with portal hypertension usually have values ≥ 1.1 mg/dL whereas patients with noncirrhotic ascites usually have serum-ascites albumin gradients < 1.1 mg/dL.

Treatment
Bed rest and dietary sodium restriction have been the cornerstones of therapy for ascites. Recumbence decreases activation of renin, angiotensin and aldosterone, decreases sympathetic output, and increases glomerular filtration rate and sodium excretion. Reduction of sodium intake is the other major component of ascites management. Since 20% of cirrhotics with ascites excrete relatively high amounts of sodium in the urine, reducing the sodium content in the diet to 40-60 mEq/day is effective. In patients with low urinary sodium excretion, negative sodium balance usually cannot be obtained without the aid of diuretics.

The goal of diuretic therapy in cirrhotics with ascites is to promote a safe and sustained diuresis. Loop diuretics alone give a good naturesis in only 50% of cirrhotics with ascites. In contrast, spironolactone is followed by a good naturalistic response in most patients. Azotemia secondary to intravascular volume depletion is a common complication of diuretic therapy. Other complications include hyponatremia, muscle cramps, decreased libido, gynecomastia and hepatic encephalopathy. Patients who do not respond to salt restriction and a diuretic regimen are considered diuretic-resistant. However, it is important to search for overlooked sources of sodium intake such as sodium-rich antacids and intravenous antibiotics. In addition, NSAIDS and beta blockers, both of which interfere with renal sodium excretion, should be avoided, if possible.

Therapeutic paracenteses and peritoneovenous shunts can be used in patients in whom diuresis cannot be achieved safely with sodium restriction and diuretics. Repeated large volume paracenteses are more effective than diuretics in removing ascites from such patients. Hyponatremia, azotemia, and hepatic encephalopathy also are less frequent. Furthermore, complete removal of ascites with a single paracentesis has a complication rate similar to that seen with repeated large-volume paracenteses.

The peritoneovenous shunt produces sustained blood volume expansion by continuously shunting ascites to the central circulation. Peritoneovenous shunts are associated with many complications including bacterial infection, diffuse intravascular coagulation, pulmonary edema, esophageal variceal hemorrhage, and congestive heart failure. Nevertheless, they have been shown to be as effective as large volume paracentesis in the management of patients with diuretic resistant ascites. Transjugular shunts also can be effective in patients with refractory ascites. Since the 12 month survival of patients with ascites refractory to diuretics is only 40%, these patients should be considered for possible liver transplantation.

INFECTIONS
Spontaneous bacterial peritonitis (SBP) accounts for 60%-70% of all serious infections in patients with cirrhosis. The organisms most frequently cultured are E. coli, Streptococci, klebsiellae and enterococci. Anaerobes rarely cause SBP. The mortality associated with SBP is 50%; moreover, those who recover have a 70% chance of a recurrent episode within a year. It is important to differentiate spontaneous peritonitis from intestinal perforation with secondary peritonitis. The clinical features of each may be quite similar; however, patients with intestinal perforation usually have lower ascitic fluid glucose levels, higher LDH levels, and higher total protein concentrations than patients with spontaneous peritonitis. In addition, patients with perforation often grow multiple organisms in contrast to the single organism usually cultured in patients with spontaneous peritonitis.
Most patients with infected ascites have neither fever nor abdominal tenderness; a diagnostic paracentesis is required for diagnosis. Placing ascitic fluid in blood culture bottles at the bedside significantly improves the yield of bacteria. The number of polymorphonuclear leukocytes in the ascites is the best laboratory indicator of SBP. Patients with PMN counts greater than 250/mm³ should receive empirical antibiotic therapy. The addition of albumin to antibiotics reduces the risk of renal failure and mortality in these patients. In the past empirical therapy often included ampicillin and an aminoglycoside; however the high risk of aminoglycoside nephrotoxicity limited their usefulness. Cefotaxime is more effective than ampicillin and aminoglycosides and is not nephrotoxic. A five day course is as effective as 10-14 days of treatment. Ceftriaxone and ampicillin-clavulanic acid also have been shown to be effective. Once culture results are available, antibiotic therapy can be tailored to the organism recovered. The high risk of recurrent infections which can be reduced with norfloxacin prophylaxis.

Pneumonia, septicemia and endocarditis also are common in patients with liver failure. In addition, almost a quarter of patients admitted with gastrointestinal bleeding develop bacterial infections. A 7 day course of oral antibiotics results in improved survival in these patients and has become the standard of care.

LIVER TRANSPLANTATION
The major indications for liver transplantation include: (1) cirrhosis secondary to chronic hepatitis B or C virus infection or autoimmune chronic hepatitis; (2) biliary cirrhosis due to primary biliary cirrhosis, primary sclerosing cholangitis, or biliary atresia; (3) metabolic diseases including Wilson’s disease, alpha-1-antitrypsin deficiency, and hemochromatosis; (4) fulminant hepatitis; (5) alcoholic liver disease, and hepatocellular carcinoma.

Contraindications to transplantation include: (1) active infection outside the biliary tree; (2) extrahepatic malignancy; (3) advanced cardiopulmonary disease; and (4) acquired immunodeficiency syndrome (although this is being re-examined).

A simplified system for allocating donor organs has been adopted in which patients are transplanted on the basis of severity of liver disease, using a prognostic model for calculating 3 month predicted survival without transplantation.

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