HALT-C Management Guidelines:

Depression, HCC Screening, Portal Hypertension

Guidelines for the management of depression, screening for hepatocellular carcinoma (HCC) and portal hypertension have been developed for HALT-C Trial patients.

1. Depression

Background

Mood disorders (i.e., depression and anxiety) are common and problematic side effects of IFN. Mood disorders may develop during the first few months of treatment or later during long-term therapy. Mood disorders can develop in individuals without a prior psychiatric history and present with subtle signs and symptoms such as fatigue, withdrawn behavior, poor appetite, irritability, or sleep disturbance. Although IFN dose reduction and anti-depressant medications have proven useful, severe and life-threatening neuropsychiatric toxicity including attempted and completed suicide have been reported (1-3). Therefore, a heightened awareness of depression and its potential impact on patient safety and compliance is necessary when prescribing interferon.

Detection of Depression

In the HALT-C Trial, the CIDI will be administered pretreatment and the Beck Depression Index-II (BDI-II) will be administered every 3 months during treatment. In order to provide rapid and reliable psychiatric services for enrolled patients, a collaborative psychiatrist/ psychologist should be identified in each center for urgent and elective referrals.

CIDI

The CIDI-Auto 2.1 is the computerized version of the Composite International Diagnostic Interview (CIDI) developed by the World Health Organization (4). The CIDI is a comprehensive, fully standardized interview that can be used to assess mental disorders and provide diagnoses according to the definitions and criteria of the ICD-10 and DSM-IV (See Attachment 1). The CIDI can be administered by trained study personnel, does not require outside informants or medical records, and can be completed in 20-40 minutes.

Beck Depression Index-II (BDI-II)

The BDI-II is a 21 item, self-administered survey used to screen for and monitor depression that takes 5-10 minutes to complete (5). The BDI-II has been shown to provide valid and reliable information in follow-up studies of patients with either psychiatric illness or medical illness (6,7). Although no arbitrary scores are available that can be used on all patients to classify the severity of depression, specific interpretation guidelines are available (8). The BDI-II was developed for the assessment of symptoms corresponding to DSM-IV criteria for diagnosing depressive disorders in 1996. The BDI-II has been extensively tested and validated and is felt to be an improvement over the previous versions of the Beck (9).

Screening

1. Subjects with the following psychiatric disorders will be excluded from the trial:
   - Suicide attempt or hospitalization for depression within the past 5 years
   - Any current (within 6 months) severe or poorly controlled psychiatric disorder (e.g., depression, schizophrenia, bipolar illness, obsessive-compulsive disorder, severe anxiety, personality disorder).
2. The following patients must be assessed and followed (if recommended) by a psychiatrist or other mental health professional. Those patients unwilling to be assessed and followed in this manner will not be eligible for the trial.

- Patients who have had a suicide attempt and/or hospitalization for depression more than 5 years ago.
- Patients who have had severe or poorly controlled psychiatric disorder (e.g., depression, schizophrenia, bipolar illness, obsessive-compulsive disorder, severe anxiety, personality disorder) more than 6 months ago but less that 5 years ago.

3. At Screen 1, eligible subjects with a history of severe or dose limiting-neuropsychiatric toxicity during prior interferon treatment should be referred to the collaborative psychiatrist/ psychologist. In addition to clarifying possible psychiatric disorders, the consultant may advise on the need for adjuvant medical or counseling therapy and suitability for enrollment in the HALT-C Trial.

4. During Screening, all eligible subjects will complete the Anxiety, Depression, Alcohol, and Substance Abuse modules of the CIDI auto 2.1, except sites with special difficulties (see G.3.c.)

5. Subjects with a DSM-IV diagnosis of recent panic disorder, recent generalized anxiety disorder, and recent major depression from the CIDI should be evaluated by the Principal Investigator or physician co-investigator (See Attachment 1, page 58).

6. At Screen 2 all eligible subjects will complete the BDI-II (see below).

Monitoring of Depression

1. Potential mood disturbance/medication intolerance will be assessed at each visit by study personnel.

2. Anemia, thyroid dysfunction, and other confounding medical issues should be evaluated in any patient with a mood disorder or abnormal BDI-II score.

3. The BDI-II will be self-administered at Screening and every 3 months to month 54. It will be scored and interpreted locally at each study visit and the score will be recorded in the HALT- C database (Form #44).

4. The BDI-II is scored by summing the ratings for 21 items. Each item is rated on a 4-point scale ranging from 0-3.

5. Subjects with abnormal BDI-II scores (range: 11 to 63 with higher scores indicative of more severe symptoms) should be assessed and managed as follows:

BDI-II score	Clinical Picture
0 – 10	None to minimal depression
11 - 14	Mild depression
15 - 19	Moderate depression
20 - 28	Severe depression
≥29	Critical depression

6. Practitioners should keep in mind that all self-report inventories are subject to response bias. That is, some individuals may endorse more symptoms then they actually have and thus produce spuriously high scores while others might deny symptoms and receive spuriously low scores. In addition, the practitioner is cautioned that the BDI-II may simply reflect the degree of depression, not the diagnosis of depression. Determination of the severity of depression and the establishment of a diagnosis of depression require examination by a clinician (physician or psychologist/ psychiatrist).

7. Because the BDI-II total score provides only an estimate of the overall severity of depression, it is important to be attentive to specific items regarding suicidal ideation. Patients admitting to suicide ideation **(Item 9)** and hopelessness **(Item 2)** with a **rating of 2 or 3** should be closely scrutinized for suicide potential.

8. Any patient who develops recurrent suicidal ideation, a suicide plan and/ or makes a suicide attempt should have IFN immediately discontinued and be referred to a psychiatrist for further management.

9. Suggested guidelines for interferon dose reduction:
   - Unpleasant and/or disabling side effects might prompt dose reduction, but this is not required.
   - A BDI score of 20-28 or a score of 15-19 that has doubled since the previous measurement might prompt further attention from the PI, but is not a requirement for dose reduction.
   - A score of >29 or higher should prompt attention from the PI and dose reduction or discontinuation should be considered.

10. Suggested guideline for withholding/discontinuing interferon:
    - Persistent suicide ideation/suicide plan/suicide attempt should lead to discontinuation of interferon.

11. Follow-up telephone contact is recommended for all patients within 2 to 4 weeks if:
    - BDI-II > 15
    - anti-depressives are started
    - interferon is reduced due to psychiatric toxicity

Anti-depressants

1. For subjects with moderate or severe depressive symptoms or with a BDI-II score of > 15, anti-depressives should be used before considering interferon dose reduction, whenever possible.

2. Subjects requiring anti-depressants will likely require additional telephone follow-up and clinic visits for depression assessment per local PI.

3. Anti-depressant medication selection will be determined by patient tolerance and physician preference.

4. The following table provides information on 2 available anti-depressants which may be of use in treating interferon induced depressive symptoms:

Drug	**Citalopram** (Celexa, P-D)	**Venlafaxine XR** (Effexor XR, Wyeth)
Starting dose	20 mg qd	37.5 mg qd (50% in cirrhosis)
Maximum dose	60 mg qd	150 mg qd
Mechanism of action	Selective SSRI	SSRI and norepi reuptake inhibitor
Side effects	Dry mouth, nausea, sleep disturb	Anxiety, sweating, nausea
Advantages	Once a day	Once a day
Precautions	CYP3A4 drug interactions: avoid MAO inhibitors	CYP2D6 drug interactions: avoid MAO inhibitors
Drug cost 1 month	$78	$75

Psychiatric referral

Referral to the identified local psychiatry collaborator should be considered if patients develop mood disturbance refractory to anti-depressants or other interventions and/or suicidal thoughts or intent.

Depression References

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2. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. *Hepatology* 1997; 26(Suppl): 112S-121S.
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4. Wittchen HU. Reliability and validity studies of the WHO Composite International Diagnostic Interview: A critical review *J Psychiatric Research* 1994; 28: 57-84.
5. Beck A, Ward C, Mendelsohn M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561-571.
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Attachment 1

DSM-IV Diagnosis from CIDI-Auto 2.1 Interview

Anxiety disorders

- Specific phobia
- Social phobia
- Agoraphobia without history of panic disorder
- * Panic disorder without and with agoraphobia
- * Generalized anxiety disorder

Depressive disorders

- * Major depression, single episode (subtypes: mild, moderate, severe)
- * Major depression: recurrent (subtypes: mild, moderate, severe)
- Dysthymia

Alcohol abuse

Alcohol dependence

Psychoactive substance use disorders; dependence or abuse

Cannabis	Opioid	Inhalant
Cocaine	Sedatives	PCP
Hallucinogen	Stimulants	Amphetamine or similar-acting substance

Others (not otherwise specified [NOS])

2. HCC Screening

Introduction

The purpose of obtaining the Screening AFP and ultrasound (U/S) is to document that hepatocellular carcinoma (HCC) is not present during the Screening period. A normal AFP and absence of a defect by U/S is strong evidence against the presence of HCC.

The higher the AFP, the more likely that undetected HCC is present. However, 20–30 % of patients with HCV uncomplicated by HCC will have elevations of AFP above the normal range. Most of these elevations are relatively low (< 75 ng/ml) and stable. Stable levels are defined as less than twice the initial value over 28 days or more. Furthermore, stable values between 75 and 200 ng/ml are often not due to HCC if the levels are not rising and the U/S is negative for a defect.

Testing Schedule

AFP testing is to be performed at Screen 1, baseline, and every three months. Ultrasound is to be performed during Screening (if not performed during the previous 6 months), at week 20, and then at months 12, 24, 36, and 48 for randomized patients.

AFP Monitoring during Screening

1. If the AFP is between ULN and 75 and the ultrasound is normal, then the patient is eligible for the Lead-in.
2. If the AFP is between 76 and 200, then the ultrasound must be normal and an MRI or CT must be normal for the patient to be eligible for the Lead-in.
3. If the AFP is > 200, then the patient is not eligible for the Lead-in.
4. If the Screening AFP for Express patients is between 200 and 1000, the ultrasound must be normal and an MRI or CT must be normal for the patient to be eligible for enrollment.
5. If for some reason the required tests cannot be performed within the time limit from Screening Visit 1 to baseline, then the site may submit a formal request to the Exemption Committee to extend the visit window.

AFP Monitoring during the Lead-in and Randomized Phases

A doubling of screening or baseline value or a value of >200 should trigger concern about possible HCC and require additional workups:

1) AFP testing: Perform AFP testing monthly until there is a 50% decrease or it remains stable for 3 months.

2) Ultrasound:
   a) If the ultrasound was performed in the previous 3 months, perform triphasic CT or MRI.
   b) If the ultrasound was not performed within the last 3 months, repeat the ultrasound.
   c) If the repeat ultrasound shows new defect, perform triphasic CT or MRI.
   d) If the repeat ultrasound shows no defect and AFP continues to rise:
      - Perform triphasic CT or MRI
      - If triphasic scan or MRI are negative for HCC, perform monthly AFP until there is a >50% decline or it remains stable over 3 months, or if elevated, repeat MRI.

3. Portal Hypertension

Introduction
Portal hypertension is a major complication of cirrhosis and contributes substantially to cirrhosis-related morbidity and mortality, which are important endpoints for the HALT-C Trial. It is therefore important that the management of portal hypertension in patients enrolled in this trial be standardized across treatment centers and treatment arms. Such management will be considered below in the context of the natural history of portal hypertension and variceal hemorrhage:

Management of patients who have never bled from varices before (Attachment 2)
The plan of management of such patients will depend on the histologic stage of their disease. Clinically significant portal hypertension does not occur in patients with hepatitis c until cirrhosis develops. Therefore all patients will undergo a diagnostic endoscopy within 4 weeks of randomization (unless one has been done within the last 12 months).

Initial endoscopy: The objective of this initial baseline endoscopy will be to document the presence or absence of esophageal varices, gastric varices and portal gastropathy. This will provide valuable baseline data that will be used for comparison with findings from subsequent endoscopies.

1. Methods: Panendoscopy will be performed using conscious sedation in most cases. Appropriate safety guidelines, as defined by the American Society of Gastrointestinal Endoscopy will be used during the procedure. The following will be assessed:

    a. Esophageal varices will be assessed in the distal 5 cm of the esophagus with air-insufflation of the esophagus. The following parameters will be noted:
        1. # of columns of varices
        2. Extent of varices
        3. Size of varices: corresponding to F1-F3 of the NIEC classification, as below:
            Grade 0 (none): No varices present.
            Grade 1 (small): Varices that can be flattened out by insufflation.
            Grade 2 (medium): Varices that cannot be flattened out by insufflation and which occupy less that 33% of the lumen of the esophagus.
            Grade 3 (large): Varices that occupy more than 33% of the lumen of the esophagus.
        4. Red signs: red wale marks, cherry red (hematocystic) spots, varix on varix.

    b. Gastric varices will be identified and classified according to Sarin's classification as:
        1. Gastro-esophageal varices (GOV) type 1: Gastric varices in continuity with esophageal varices along the lesser curve of the stomach.
        2. Gastro-esophageal varices (GOV) type II: Gastric varices in continuity with esophageal varices along the greater curve of the stomach.
        3. Isolated gastric varices (IGV) type I: Isolated cluster of varices in the fundus of the stomach.
        4. Isolated gastric varices (IGV) type II: Isolated varices in regions of the stomach other than in the fundus.

    c. Endoscopic assessment and scoring of portal gastropathy will be defined as follows for the purposes of this study (These definitions are identical to those proposed by the NIEC (1) and by Sarin (2) to develop the scoring system for portal gastropathy presented at the Baveno conference):
        1. Mosaic pattern: small polygonal areas demarcated by a distinct white-to-yellow border and with a slight central bulge, which have a mosaic, fish scale-like appearance upon endoscopy. The mosaic pattern will be considered to be mild when the color of the mucosa

is pink while diffuse erythema (redness) of the mucosa will be considered to represent severe MP.

2. Red Marks: flat or slightly bulging red lesions seen in the gastric mucosa. Such lesions include fine punctuate hemorrhagic spots and discrete red spots corresponding to the red point lesions and cherry red spots described by the NIEC group **(**1). When present in isolated discrete spots, they will be given a score of 1 while confluent areas of submucosal hemorrhage will be given a score of 2.
3. Black-brown spots: represent old submucosal hemorrhage and will not be scored.
4. Gastric antral vascular ectasia (GAVE): will be diagnosed by the presence of flat or slightly raised red stripe-like lesions radiating from the pylorus to the antrum and body of the stomach for a variable distance (3).

Calculation of the portal gastropathy score

The severity of the portal gastropathy will be scored as proposed by Sarin (2). A mild mosaic pattern will be given a score of 1 while severe MP will be scored as 2. Isolated RM will be scored as 1 while confluent RM will be scored as 2. Absence of GAVE will be scored as 0 while the presence of GAVE will be scored as 2. The portal gastropathy will be considered to be mild when the total score is less than or equal to 3 and severe if the score is 4 or greater.

Photodocumentation of endoscopy

Photographs of each endoscopy will be taken. Two sets of photographs will be required. One set will remain on site in the patient's record. The second will be sent to the DCC for blinded review. The photographs will be reviewed in a blinded manner by a panel of endoscopists at a central location and scored separately by each member of the panel.

Management of patients following initial endoscopy:

As outlined in Attachment 2, the management of patients will depend on the findings of the initial endoscopy. Those without varices will be followed without additional interventions. All those with Grade 2 (medium) or Grade 3 (large) esophageal varices as well as gastric varices will be treated for primary prophylaxis of variceal hemorrhage as follows:

Agent to be used: nadolol or another non cardio selective beta blocker if nadolol cannot be used.

Dosage: Treatment will be initiated with 20-40 mg/day orally (once a day) and the dose titrated upwards until the resting heart rate is between 55-65 beats/min or adverse effects occur preventing further increase or continuation of therapy.

Subsequent endoscopy: will be performed at month 48 (exit) for those who have no varices at initial endoscopy. In those with varices, endoscopy will be performed again at months 24 and 48**.**These times were determined on the basis of the probability of finding differences in the two treatment arms at the different points in time from entry.

What to do for those with large varices who are intolerant of beta blockers: It is anticipated that up to 15-20% of subjects who are started on beta blockers will have adverse effects requiring discontinuation of the drug. In such cases, endoscopic band ligation may be performed at the investigators' discretion and after discussion with the patient. Such an option will be necessary because of ethical concerns about withholding potentially life-saving therapy in such subjects.

Management of active variceal hemorrhage

Management of active variceal hemorrhage or prevention of recurrent variceal hemorrhage should be performed according to the standard of care at each institution

Portal Hypertension References

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Attachment 2: Management of patients who have never bled from varices