Hepatitis B Prophylaxis for Non-Thoracic Solid Organ Transplant - Adult - Inpatient Clinical Practice Guideline

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Executive Summary

Guideline Overview

This document is intended to guide clinicians in ordering prophylaxis for hepatitis B in adults who have received a non-thoracic solid organ transplant. Guidance for both liver and non-liver transplant recipients is included.

Key Revisions January 2016

1. Addition of entecavir to guideline in management of some patients.
2. Additional indications to consult Hepatology in patients receiving HBcAb positive non-thoracic solid organ transplant

Key Practice Recommendations

Therapeutic options addressed in this guideline include selection and dosing of the following medications for the management of HBV prophylaxis following non-thoracic solid organ transplant:

1. Hepatitis B Immune Globulin (HBIG) (HepaGam B®)
2. Lamivudine (Epivir HBV® and Epivir®)
3. Entecavir (Baraclude®)

Companion Documents

- Renal Function-based Dose Adjustments – Adult – Inpatient/Ambulatory Clinical Practice Guideline
- Renal Function-Based Dose Adjustment - Adult – Inpatient/Ambulatory Delegation Protocol [8]
- Hepatitis B Prophylaxis for Non-Thoracic Solid Organ Transplant – Adult – Inpatient Delegation Protocol [118]

Scope

Disease/Conditions: Non-thoracic solid organ transplant

Clinical Specialty: Transplant, Pharmacy

Intended Users: Transplant surgeons, transplant hepatologists, transplant nephrologists, pharmacists, and transplant coordinators

CPG objectives: To guide the use of hepatitis B prophylaxis in adult patients who have received a non-thoracic solid organ transplant. Guidance for hepatitis B prophylaxis will be evaluated based on donor and recipient HBV serologies.

This guideline will review hepatitis B prophylaxis in non-thoracic solid organ transplant and will aim to provide clinical support in selecting a regimen for prophylaxis that is best suited based on recipient and donor serologic status.

Target Population: Adult patients who have received a non-thoracic solid organ transplant and the donor and/or recipient have serologic evidence of hepatitis B infection or past exposure.

Interventions and Practices Considered:

This guideline makes recommendations for the use, dosing and administration of hepatitis B immune globulin (HBIG) and antivirals in patients with or at risk for contracting hepatitis B through non-thoracic transplantation.

Major Outcomes Considered:

- Rates of hepatitis B recurrence post-transplant
- Rates of *de novo* hepatitis B post-transplant
- Resistance rates
- Treatment cost

Methodology

Methods Used to Collect/Select the Evidence:
MEDLINE was searched using the terms hepatitis B prophylaxis, liver transplant, renal transplant, hepatitis B immune globulin, lamivudine, and entecavir. References from identified articles were further evaluated. Expert opinion and clinical experience were considered during discussions of the evidence.

Methods Used to Formulate the Quality of the Evidence/Strength of the Recommendations:
The workgroup members arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees. Internal expert opinion was also incorporated into guideline development in cases of a lack of evidence or conflicting evidence.

Methods Used to Assess the Quality and Strength of the Evidence and Recommendations:
Internally developed recommendations were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1** in Appendix B).[1]

Rating Scheme for the Strength of the Evidence/Recommendations:
See Appendix B for the rating schemes used within this document.

Cost Analysis:
Cost Analysis (as of December 2016)

Medication	Cost
Hepatitis B immune globulin (312 units/mL)	$138/312 units (1 mL vial) $605/1560 units (5 mL vial)
Lamivudine 100 mg	$9.13/tablet
Entecavir 0.5 mg or1 mg	$12.36/0.5 mg tablet $15.07/1 mg tablet

Recognition of Potential Health Care Disparities: None identified

Definitions[2]

Abbreviation	Definition	HealthLink Test Code	Comments
HBV	Hepatitis B virus		
HBIG	Hepatitis B immunoglobulin		Hepatitis B immunoglobulin Lexicomp monograph
HBsAg	Hepatitis B surface antigen	HBSAG	• Surface protein found on hepatitis B virus • Presence is indicative of an infectious person • It may be elevated in both acute and chronic infection • Measured by *Hepatitis B Surface Ag (HBSAG)*
HBsAb	Hepatitis B surface antibody	HBSABI	• An antibody against hepatitis B viral surface antigen • Presence is indicative of either o Protective immunity from vaccination o Successful recovery and immunity from active infection • Measured by *Hepatitis B Surface Ab (HBSABI)*
HBcAb	Hepatitis B core antibody	HBCAB	• Antibody present at onset of acute infection and persists for life • Presence is indicative of infection with HBV in an undefined time frame • Hepatitis B core antibody measured by *Hepatitis B Core Ab, Total (HBCAB)*
HBcAb-IgM	IgM antibody to hepatitis B core antigen	XHBCM	• IgM antibody to hepatitis B core antigen indicates infection occurring in the last 6 months • Hepatitis B core antibody IgM measured by *Hepatitis B Core Ab, IgM (XHBCM)*
HB quant PCR	Hepatitis B DNA, Ultra Quant, PCR	XHBVD	• Quantitative measure of active viral replication o Active infection: >20000 IU/mL o Chronic infection: 2000-20000 IU/mL o Inactive carrier: <2000 IU/mL • Measured by *Hepatitis B DNA, Ultra Quant, PCR (XHBVD)*
CrCL	Creatinine clearance		As defined in UWHC Guidelines for Renal Function-Based Dose Adjustments in Adult Inpatients

Introduction

Hepatitis B virus (HBV) infection is the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma worldwide.[2] The early transplant experience with HBV positive patients resulted in universal recurrence and frequent graft loss due to the lack of prophylactic strategies.[3-5] The introduction of hepatitis B immunoglobulin (HBIG) and oral antiviral therapy have drastically reduced recurrence rates of HBV infection.[6] As the gap between donor availability and recipient demand continues to rise, efforts have been made to use HBV core antibody positive but hepatitis B surface antigen negative organs.[7,8] Early studies found a risk of hepatitis B transmission between 15 to 95% in liver recipients with HBV exposed allografts.[9,10] However, when HBIG and/or antiviral agents are used comparable rates of patient and graft survival to patients without donors with HBV exposure have been demonstrated.[11-13] The primary concern with use of HBV core positive grafts is the risk of *de novo* HBV infection. Without antiviral prophylaxis, *de novo* HBV infection rates range from 15% in the hepatitis-B-core-antibody-positive/ hepatitis-B-surface-antibody-positive liver recipient to approximately 50% in those without exposure (hepatitis B core antibody negative/hepatitis B surface antibody negative).[14] A combination of HBIG and lamivudine can reduce rates of *de novo* HBV infection to approximately 2.5% in those without exposure. When the newly developed potent antivirals with high barriers to genetic resistance entecavir or tenofovir are used in place of lamivudine *de novo* HBV incidence decreases to 1% or lower.[15] This risk increases in the setting of non-compliance with oral antiviral prophylaxis. Emphasis should be placed on education and strict compliance with prophylactic strategies to decrease the risk of *de novo* and lamivudine-resistant infection in the recipient.[16]

The risk of HBV transmission in non-liver organs is lower but prophylaxis is still recommended. Early studies estimate the risk of transmission from hepatitis B core antibody (HBcAb) positive donors is zero to 27% for renal transplant recipients depending on the recipient's immunity at the time of transplant. Using prophylaxis strategies the risk of *de novo* HBV post renal transplant can essentially be negated.[17-20]

It is noteworthy that there is a lack of consensus regarding appropriate hepatitis B prophylaxis post-transplant and various levels of evidence associated with indications, therefore, these guidelines are based on current evidence and local expert opinion.

Recommendations

Recipient Laboratory Testing Pretransplant (*UWHealth Strong Recommendation, Low Quality of Evidence*)

1. Standard lab orders for transplant recipient:
   - 1.1. Hepatitis B surface antigen (HBsAg)
   - 1.2. Hepatitis B surface antibody (HBsAb)
   - 1.3. Hepatitis B core antibody (HBcAb)
2. Additional labs for patients with positive HBcAb or HBsAg
   - 2.1. IgM antibody to hepatitis B core antigen (HBcAb-IgM)
   - 2.2. Hepatitis B DNA, Ultra Quant, PCR

Donor Laboratory Testing (*UWHealth Strong Recommendation, Low Quality of Evidence*)

1. Hepatitis B surface antigen (HBsAg)
2. Hepatitis B surface antibody (HBsAb)
3. Hepatitis B DNA, Ultra Quant, PCR (living donor)
4. If possible, the deceased donor liver should be biopsied and assessed for HBV DNA. However, a negative result does not rule out the possibility of the presence of HBV.[17]

Liver Recipient Transplanted for Hepatitis B Liver Disease or with Active HBV Disease at Time of Transplant (donor HBcAb [+/-], recipient HBcAb [+], HBsAg [+], or with HB quant PCR >2000 IU/mL) [14,21-24]

1. HBIG 10000 units IV once during anhepatic phase (*UWHealth Strong Recommendation, Moderate Quality of Evidence*)

2. HBIG 800 units IM (rounded to nearest vial size) daily on postoperative days one through seven; then monthly for at least 12 months or a duration at the discretion of Hepatologist. (*UWHealth Strong Recommendation, Moderate Quality of Evidence*)
3. Renally adjusted oral entecavir.[25] (*UWHealth Strong Recommendation, Moderate Quality of Evidence*)
4. Surveillance labs should be drawn monthly for 6 months, then every 2 months for 6 months, then every 3 months for 1 year, and then yearly (when monthly HBIG IM injections are discontinued restart lab cycle with monthly labs):
   4.1. Hepatitis B surface antigen (HBsAg)
   4.2. Hepatitis B surface antibody (HBsAb)
   4.3. Hepatitis B DNA, Ultra Quant, PCR

Patients receiving HBcAb positive non-thoracic solid organ transplant[8,19,20,24-26]

1. Upon admission for receipt of HBcAb-positive organ transplant the following labs should be obtained in the recipient:
   1.1. Hepatitis B core antibody (HBcAb)
   1.2. Hepatitis B surface antibody (HBsAb)
   1.3. Hepatitis B surface antigen (HBsAg)
2. Each patient should be prescribed the appropriate anti-viral therapy based on Table 1. (*UWHealth Strong Recommendation, Moderate Quality of Evidence*)
3. Hepatology should be consulted if there is evidence of active HBV infection at time of presentation for non-thoracic solid organ transplant. (*UWHealth Strong Recommendation, Very Low Quality of Evidence*)
   3.1. This includes HBsAg positive or Hepatitis B DNA, Ultra Quant, PCR >2000 IU/mL.
4. HBsAg, HBsAb, HBcAb, and hepatitis B DNA, Quant, PCR should be drawn at 1 and 3 months post-transplant. Results should be discussed at first clinic visit with a hepatologist to determine a treatment plan for continued laboratory monitoring and anti-viral therapy. Donor liver biopsy results may also be used to make treatment decisions, when available. (*UWHealth Strong Recommendation, Low Quality of Evidence*)

Hepatitis B core antibody positive recipients of any non-thoracic solid organ transplant (Donor HBcAb (-), Recipient HBcAb (+)[8,24,26]

1. Renally adjusted oral entecavir should be prescribed for all patients at the prophylactic dose. (*UWHealth Strong Recommendation, Low Quality of Evidence*)

Table 1. Hepatitis B Prophylaxis for non-thoracic Solid Organ Transplant Recipients – Quick Reference

DONOR Status	RECIPIENT Status				
HBcAb[A]	HBcAb[A]	HBsAb[B]	HBsAg[C]	**Interpretation of Donor Status and Recipient Status**	**Prophylactic Regimen**
POS	NEG	NEG	NEG	Recipient has no protective immunity and is susceptible to infection	**Liver allograft** (1) HBIG 10000 units IV once during anhepatic phase (2) Entecavir indefinitely (3) Provide HBV vaccine at the 6 months transplant follow-up appointment **Renal/pancreas allograft** (1) Entecavir for one year (2) Provide HBV vaccine at the 6 months transplant follow-up appointment
POS or NEG	POS	POS	NEG	Immune due to natural infection	Entecavir for one year[D]
POS	NEG	POS	NEG	Immune due to vaccination	**Liver allograft**: entecavir indefinitely **Non-liver allograft**: entecavir for one year
POS or NEG	POS	NEG	POS	Acute or chronically infected Use IgM antibody to hepatitis B core antigen (HBcAb-IgM) to determine stage: • If IgM POS ➔ acute infection • If IgM NEG ➔ chronic infection	**Liver allograft** (1) HBIG 10000 units IV once during anhepatic phase (2) HBIG 800 units IM (rounded to nearest vial size) daily on postoperative days one through seven; then monthly for at least 12 months or a duration at the discretion of Hepatologist (3) Entecavir indefinitely **Renal/pancreas allograft** Chronic: Entecavir indefinitely Acute: consult Hepatology
POS or NEG	POS	NEG	NEG	Four possibilities: 1. Resolved infection ("inactive carrier" state) 2. False POS Hep B core antibody 3. "Low level" chronic infection 4. Resolving acute infection	**All allografts** (1) Repeat HBV serologies (HBcAb, HBsAb, HBsAg, Hepatitis B DNA) (2) Entecavir until repeat serologies (3) Based on repeat serologies, provide antiviral prophylaxis as described in Table 1. **Liver allograft** (1) If donor **HBcAb NEG**: entecavir x 3 months. HBV vaccination at 6 months (2) If donor **HBcAb POS**: HBIG 10000 units IV once during anhepatic phase, entecavir indefinitely. HBV vaccination at 6 months.

[A] *Hepatitis B core antibody (HBcAb)*: This antibody is present at onset of acute infection and persists for life. Its presence indicates infection with Hepatitis B virus in an undefined time frame. To further delineate the infectious time line, an IgM antibody to hepatitis B core antigen can be ordered. If positive, this would indicate acute infection (infection occurring in the last 6 months).

[B] *Hepatitis B surface antigen antibody (HBsAb):* The body produces antibodies against hepatitis B surface antigen. The presence of HBsAb indicates either protective immunity from vaccination or successful recovery from active infection with subsequent immunity. Protective immunity corresponds to HBsAb >10 mIU/mL.

[C] *Hepatitis B surface antigen (HBsAg)*: This is a protein found on the surface of the hepatitis B virus. Its laboratory presence indicates an infectious person. It can be elevated in both acute and chronic infection.

[D] For liver allografts, check HBsAb status of recipient at one year and discontinue entecavir only if HBsAb >10 mIU/mL.

[E] Usual infusion rate of HBIG is 2 mL/min. During anhepatic phase, infusion rate may be increased to 4 mL/min to complete infusion prior to liver allograft placement.

UW Health Implementation

Potential Benefits:
The predominant benefit of implementation of this guideline is the standardize care for hepatitis B prophylaxis after transplantation of a non-thoracic solid organ.

Potential Harms:
The risk of implementing this guideline and administering HBIG and/or lamivudine is increased risk of infusion-related reactions and neutropenia.

Qualifying Statements:
There is a lack of consensus regarding the appropriate hepatitis B prophylaxis regimen post-transplant and various levels of evidence, therefore, these guidelines are based on current evidence and local expert opinion. The recommendations included in this guideline are subject to change with publication of additional evidence.

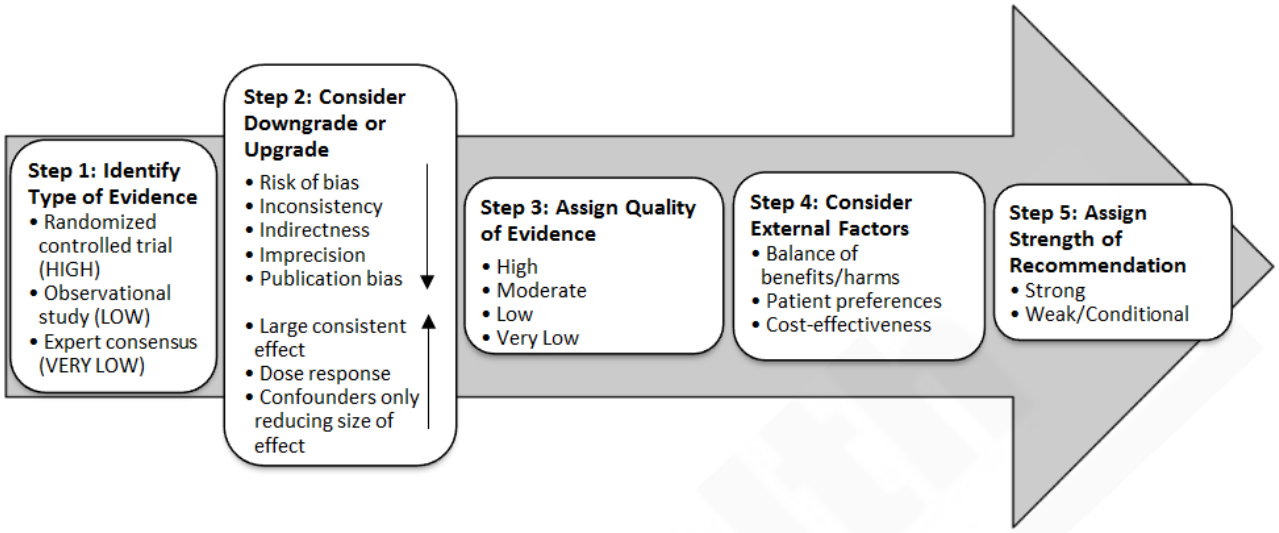
Guideline Metrics:
- Adherence to evidence based utilization of HBIG
- Recurrent and *de novo* hepatitis B rates post-transplant

Implementation Plan/Tools
1. Guideline will be posted on U-Connect in a dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations (such as the following) will be reviewed for consistency and modified as appropriate.

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Appendix A. Evidence Grading Scheme

Figure 1. GRADE Methodology adapted by UW Health[1]



GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Appendix B. Hepatitis C Positive Donor Into Hepatitis C Negative Solid Organ Transplant Recipient Treatment – Quick Reference

From: Hepatitis B Prophylaxis for Non-Thoracic Solid Organ Transplant – Adult – Inpatient Clinical Practice Guideline

Last Reviewed: 8/2019; Last Updated: 8/2019

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Background:

To increase the available number of organs for donation, transplanting organs from hepatitis C virus (HCV)-infected donors into uninfected patients has become a standard of care offering at some transplant centers. Small trials have investigated this approach in liver, kidney, heart, and lung transplantations and demonstrated success.[1-5]

These tables are meant to provide guidance for the prophylaxis and treatment of HCV in HCV naïve recipients who undergo liver, kidney, heart, and lung transplantation from a hepatitis C+ donor (either antibody or PCR positive). All recommendations are (*UW Health Conditional Recommendation, Low Quality of Evidence*)

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Table 1. Recommended therapy for HCV Antibody (+) and NAT (+) donors into HCV-negative recipients

	Liver	Kidney	Heart	Lung
First Line Therapy and Duration[A]	Glecaprevir (300 mg) and pibrentasvir (120 mg) x 12 weeks	Glecaprevir (300 mg) and pibrentasvir (120 mg) x 4 weeks[B]	Sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks[B]	Sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks[B]
Initiation of therapy[C]	Once patient is clinically stable and prior authorization is approved	Post-op day #0 – following transplantation	Post-op day #0 – following transplantation	Post-op day #0 – following transplantation
If Acute Kidney Injury Occurs	No Change – Continue glecaprevir (300 mg) and pibrentasvir (120 mg) x 12 weeks	No Change – Continue glecaprevir (300 mg) and pibrentasvir (120 mg) x 4 weeks	No Change – Continue sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks	No Change – Continue sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks
If Declared ESRD on Chronic Dialysis	Consult Hepatology	No Change – Continue glecaprevir (300 mg) and pibrentasvir (120 mg) x 4 weeks	No Change – Continue sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks, if duration of therapy is extended past 4 weeks consult Hepatology	No Change – Continue sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks, if duration of therapy is extended past 4 weeks consult Hepatology
If Unable to Swallow Oral Dosage Forms	Initiation should occur when patient is stable with a reliable oral route. • If ≤1 week, crush and administer glecaprevir (300 mg) and pibrentasvir (120 mg) • If >1 week, consult Hepatology	Hold therapy until patient regains ability to swallow, then resume and extend duration to 12 weeks	No Change – continue sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks	No Change – Continue sofosbuvir (400 mg) and velpatasvir (100 mg) x 4 weeks
If Insurance Requires Non-First Line Therapy Above	N/A – Patient will be initiated after coverage determined	Switch to covered direct-acting antiviral at discharge and complete a total of 4 weeks	Switch to covered direct-acting antiviral at discharge and complete a total of 4 weeks	Switch to covered direct-acting antiviral at discharge and complete a total of 4 weeks

Glecaprevir-pibrentasvir: Mavyret®

Sofosbuvir-velpatasvir: Epclusa®

[A] Following completion of therapy, HCV PCR should be updated at 12 and 24 weeks post-treatment.

[B] Extend duration to 12 weeks if unable to begin on POD #0 or if any interruption in therapy.

[C] HCV Genotype and PCR on post-op day 1, 3, 5, and then every three days until positive. Prior authorization should be initiated as soon as recipient PCR is positive.

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