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World Health Organization

Global Hepatitis Programme

Guideline development for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B

PICO QUESTIONS for the WHO Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B

PICO questions

PICO 1a Vaccination	**Among persons at high risk of acquisition of hepatitis B, what are the most effective hepatitis B screening and vaccination strategies?**
P	Household and sexual contacts of HBsAg-positive persons (includes HIV-infected and HIV-negative or unknown HIV status)
I	Different active screening and hepatitis B vaccination strategies
C	No active screening or HBV vaccination
O	New HBsAg-positive transmissions among contacts; identification of existing HBsAg-positive cases; number of cases referred for care; number of cases referred for vaccination; number completed vaccination course; number hepatitis B immune; potential harms of screening (disclosure, stigmatization); cost; cost-effectiveness

PICO 1b Vaccination	**Among HIV-infected persons, what are the most effective hepatitis B vaccination strategies?**
P	HIV-positive adults, adolescents and children
I	Any hepatitis B vaccination strategy (e.g. double dose, additional booster doses, decreased dose interval)
C	Any hepatitis B vaccination strategy (including different time intervals) or no vaccination
O	Immunogenicity (sAb titre); HBV DNA positivity; HBeAg seropositivity; HBsAg seropositivity; adverse events of vaccination (any); cost-effectiveness

PICOT 2a Who to Treat?	**Among HBsAg-positive persons, what factors/tests best identify individuals at highest risk of progression, as well as those at very low risk of progression?**
P	HBsAg-positive persons
I	Key permutations of key baseline risk factors from studies of prognosis: clinical factors only (age, cirrhosis/fibrosis); clinical plus ALT: clinical plus ALT and HBV DNA: Sample stratifications include: age >40 vs <40 years; HBeAg-positive vs -negative; cirrhosis (compensated or decompensated) vs no cirrhosis; fibrosis (METAVIR 1-3) vs no fibrosis; HBV DNA (any positive or unknown, or >2000 or >20 000 IU/mL or $>10^6$ copies/mL) vs undetectable; ALT (>2x ULN or >ULN) vs normal
C	Absence of these baseline factors
O	Liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma); progression of liver disease; mortality
T	Annual progression and mortality

PICOT 2b Who to Treat?	**Among HBsAg-positive persons, what factors/tests best identify individuals with greatest benefit of treatment, and least benefit from treatment in those with and without access to laboratory tests?**
P	HBsAg-positive persons stratified according to key baseline prognostic factors and : clinical factors only (age, cirrhosis/fibrosis); clinical plus ALT: clinical plus ALT and HBV DNA: sample stratifications include: Age >40 vs <40 years; HBeAg positive vs. negative; cirrhosis (compensated or decompensated) vs no cirrhosis; Fibrosis (METAVIR 1-3) vs no fibrosis; HBV DNA (any positive or unknown, or >2000 or >20 000 IU/mL or $>10^6$ copies/mL) vs undetectable; ALT (>2x ULN or >ULN) vs normal
I	HBV antiviral treatment
C	No HBV treatment
O	HBeAg seroconversion; HBsAg loss; undetectable HBV DNA; liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease); progression of liver disease;

	reversion of fibrosis stage; mortality; severe adverse effects; antiviral resistance
T	Annual progression and mortality

PICOT 3a What treatment to use?	**What is the most effective regimen for the treatment of chronic hepatitis B infection?**
P	Treatment-naïve HBsAg-positive persons (stratified by HIV status, and different permutations of baseline risk factors from treatment studies, including HBeAg status, present or absence of cirrhosis, fibrosis stage, HBV DNA level
I	HBV treatment with highly active medicines and a high barrier to resistance (tenofovir and entecavir)
C	HBV treatment with other medicines with a low barrier to resistance (lamivudine, telbivudine or adefovir)
O	HBeAg seroconversion; HBsAg loss; undetectable HBV DNA; liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease); progression of liver disease; reversion of fibrosis stage; mortality; severe adverse effects; antiviral resistance; cost; cost-effectiveness
T	Annual progression and mortality

PICOT 3b Management of treatment failure	**What is the most effective regimen for management of treatment failure?**
P	HBsAg-positive persons previously treated with HBV regimens with a low barrier to resistance (lamivudine, telbivudine or adefovir)
I	HBV treatment with highly active medicines and a high barrier to resistance (tenofovir and entecavir)
C	Continuation of HBV treatment regimens with a low barrier to resistance (lamivudine, telbivudine or adefovir)
O	Liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease); progression of liver disease; reversion of fibrosis stage; mortality; HBeAg seroconversion; HBsAg loss; undetectable HBV DNA; severe adverse effects; antiviral resistance; cost; cost-effectiveness
T	Annual progression and mortality

PICOT 4 Treatment duration	**What criteria should be used to decide when to stop treatment?**
P	HBsAg-positive persons receiving HBV treatment
I	Different criteria for discontinuation of HBV treatment (HBeAg seroconversion, HBsAg loss, undetectable HBV DNA)
C	Continuation of HBV treatment for 1, 2, 3, 4, 5 years or more
O	Liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease); progression of liver disease; mortality; HBeAg reversion and hepatitis flare; severe adverse effects; antiviral resistance

PICOT 5a Monitoring	**What is the optimal frequency of monitoring for disease progression?**
P	HBsAg-positive persons stratified according to baseline disease stage (cirrhosis, fibrosis stage, eAg status, HIV status)
I	Annual clinical evaluation or symptom-based referral
C	Six-monthly comprehensive evaluation with fibrosis assessment, ALT, eAg status and HBV DNA
O	Liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease); progression

	of liver disease; mortality at different time points

PICOT 5b Monitoring	What is the optimal nature and frequency of monitoring for toxicity in patients receiving tenofovir?
P	HBsAg-positive persons receiving tenofovir stratified by age, gender, pregnancy status, HIV status and baseline disease stage (cirrhosis, fibrosis stage)
I	Symptom-based referral versus laboratory/other monitoring
C	Laboratory/other monitoring
O	Renal impairment, bone mineral density decline (osteoporosis, osteopenia)

PICOT 6 Monitoring for HCC	What is the most effective monitoring strategy to identify HCC early in people with chronic HBV?
P	People with chronic hepatitis B viral infection, defined by the persistence of HBsAg for more than six months
I	Screening using the following methods or combinations: liver ultrasound scan (USS); serum alpha-fetoprotein (AFP); liver USS and serum AFP
C	The screening interventions listed above or no intervention
O	New diagnosis of hepatocellular carcinoma; disease-specific mortality; all-cause mortality; lesion or hepatocellular carcinoma size (< 3cm in diameter; ≥ 3cm in diameter); liver cancer stage; cost-effectiveness

PICOT 7 PMTCT	What is the most effective antiviral therapy during the third trimester of pregnancy, to reduce transmission of HBsAg?
P	Pregnant women in the third trimester of pregnancy (defined as 27–40 weeks gestation) with chronic hepatitis B virus infection (positive for HBsAg persistently for more than 6 months) (stratified by HBeAg status)
I	Maternal treatment with the following drugs or drug combinations during third trimester of pregnancy (with or without use of birth dose vaccine): tenofovir; lamivudine; telbivudine; emtricitabine plus tenofovir/tenofovir plus emtricitabine; entecavir; adefovir)
C	Interventions listed above versus each other (either as monotherapy or combination therapy), placebo or no intervention
O	Newborn (0–9 months) and infant (9–15 first months) HBV DNA positivity; newborn and infant HBeAg seropositivity; newborn and infant HBsAg seropositivity; congenital abnormalities; adverse events (maternal (any); infant (any); infant (serious adverse events); cost-effectiveness

PICOT 8 Non-invasive assessment of liver disease stage	How should staging of liver disease be carried out in persons with HBV infection?
P	Persons with chronic hepatitis B infection
I	Non-invasive assessment of liver fibrosis using FIB-4, APRI (AST-to-platelet index), FibroTest or FibroScan
C	Liver biopsy
O	Diagnostic accuracy of non-invasive tests for staging fibrosis