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OVER VIEW ON HEPATITIS B AND HEPATITIS B VACCINE

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Abstract

World HealthOrganization (WHO) estimates 257 million people were having chronichepatitisBvirus (HBV)infection.GreatestHBVprevalencewasfoundintheWHOWesternPacificRegion.TheHepatitisBvirusvaccineisthemagnificentprotectionagainstchronicHBVinfectionanditscomplications.Globally,routineinfantimmunizationagainstHBVhasincreasedwithanestimatedcoverageof84% in 2017. The efficacy oftherapeutic vaccine seemsto improve by combination therapies.

Keywords: HepatitisBvirusinfection,Vaccination,Therapeuticvaccine,Chronic hepatitisB

Introduction

HepatitisBvirusinfection (HBV)isa dangerousinfection that isamong the topten healthproblemsintheworld[1,2].Since manypeopleareunawarethattheyhaveHBVinfection,itisconsideredoneofthesilentkillers[3].HBVinfectionisdistributedbydealingwithaninfectedperson'sbloodorotherbodyliquids.Unsafe sex,aswellashaving atattoo, piercing,ormanicure/pedicure inareaswithpoorhygienicconditionsforutensilslikeclippersandscissors,couldputpeopleindanger.HBVinfectioncanleadtosevere healthissuesincluding livercancer,cirrhosis,and liverdisease, whichcanlead to death[4].

About two billion individualshavebeen infected with HBV, whether they are chronic carriersorhavehadaprior infection.FulminatinghepatitisisacomplicationofacutehepatitisB.ChronicHBVcauses700,000 deathsperyearbecauseitcanlead to hepatocellularcarcinoma, livercirrhosis,andliverdiseaseevenintheabsenceof cirrhosis[5, 6]Theprimarymarkerfordetecting thepresenceofinfection ishepatitisBsurface antigen(HBsAg).Italsoaidsinthescreeningandanalysisofthevirus'soccurrence in a particularregion orwithin aspecific group ofpeople[7].

RenderingtotheWorldHealthOrganization(WHO),about257millionindividuals hadchronichepatitisBvirus(HBV)infectionin2015(describedashepatitisB surface antigen [HBsAg]positive)[8].

TheWHOWesternPacificRegion(6.2percent)and theWHOAfrican Region(6.2 percent)havethehighestincidenceofHBV infectedpeople.In theWHO Eastern MediterraneanRegion,HBVincidencewasreportedtobe3.3percent,2.0percent in theWHOSouth-EastAsiaRegion,and1.6percentintheWHOEuropeanRegion. TheWHORegionoftheAmericas[1] had the lowestprevalenceof HBV-infected people (0.7 percent)[8].

In2017,theEuropeanUnionandMemberStatesoftheEuropeanEconomicArearecorded26.907 casesofHBVinfection,with9%being acute, 58percentchronic, 32 percent‘unknown,' and 1%unableto be identified[4].

TheprevalenceofHBVinfectioninprisonerswasfoundtorangefrom1.4percentto

23.5percentinmanytrials.Specifically,WestandCentralAfricanprisonershadthegreatestincidenceofHBsAg(23.5percent).ChronicHBVinfectionhasalsobeenrecognizedatelevatedlevelsinEasternandSouthernAfrica(5.7%),aswellasEasternEuropeandCentralAsia(10.4percent).WhileNorthAmericahadthe lowest incidence(1.4 percent)[9].

HBVwasclassifiedasintermediatelyendemicinEgypt in2010,with prevalence ranging from3to 11%, mostlyin males[10].

HepatitisB viruscanbepassedonacrossthegenerations.HepatitisB infection in pregnantwomen may passon to theirunborn child during pregnancy orchildbirth [11].ThisislinkedtoalackofunderstandingofhepatitisBand theabsenceofHBV screeninginantenataltreatmentunits[12].

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

The anti-hepatitisBvirusvaccination

HepatitisBvaccine isthebestdefenseagainstchronicHBVinfectionandits complications,and it is included in manycountries'annualchildhoodvaccines.TheHBVvaccinehasbeenavailablesince1982andbecamewidelyavailableafter2000, buttoday'sadultscouldnothave received thevaccineaschildren.Thevaccineis highlyeffective, with threedosesproviding protection forat least20 years. In developedcountries, thevaccinehasconsiderably reduced the incidenceofHBVand its socioeconomic effects[8].

TheWorldHealthOrganizationadvisesthatallbabiesgettheHBVvaccineassoon aspossible afterbirth,usually within24 hours.Theglobalcoverage (thirddose)of routine childHBV immunizationhasimproved,withan averagecoverageof84 percent in2017. Thewidespread useofHBVvaccine can bedue to the lowincidence ofchronicHBVinfectionin childrenundertheageoffive,whichwasreportedtobe
1.3 percentin 2015[8].

Routine childhood vaccine is available in 20 (74%) of Europe's 27 countries (Belgium, Bulgaria,CzechRepublic,Cyprus,Estonia,France,Germany,Hungary, Italy,Malta, Latvia, Luxembourg, Portugal, Romania, Slovakia, Slovenia, Spain, Poland). Vaccination isexpectednotonly in infancy butalso in olderchildrenand teenagers in 12 (60%) of these countries, includingBelgium, Cyprus, Estonia, France, Germany, Italy, Malta, Latvia, Romania, Poland, and Luxembourg.Denmark, Finland, Iceland,Norway,Sweden, andtheUnitedKingdomaretheonly countries thathavenotyet implemented mandatoryhepatitisBvaccination.They havea low endemicity and considerhepatitisBto be aminorpublic health problem, so increased spending isnot justified[13].

In Italy, vaccination began in 1991 for all newborns that are requiredto be vaccinated.Adolescentswerestillvaccinatedduring the12thyearbefore2003 (12 years sincethe legislation went into effect)(the population born after1979 gotanti- HBVvaccine at the age of12 yearsbeginning in 1991)[4]InEgypt,the chanceofmother-to-child transmissioncanbe ashighas51%[14].The riskofmaterno-fetaltransmissionincreases whenthereisactivehepatitis,positive HBeAg, orhigh viralreplication [15]. Giving a newborn an injection ofhepatitis B immunoglobulin(HBVIG)andthefirstdoseofvaccinationon thefirstdayoflife,on theotherhand,reducestheriskofHBVinfectionby10%[16].HBVmayalsocause maternal mortality,particularly indevelopingcountries[17].In Egypt,regularHBV vaccination forchildren aged2, 4, and6 monthsbegan in 1992[18]. These reasons support the use ofHBsAg-based HBVscreening in antenatalcare programs[19].

Vaccination for people athigher riskfor contracting hepatitisBvirusinfection

Iftheyhadevidenceofcompletionofthe vaccinesequenceorserologicaltestsof immunity against infection, theCenters forDiseaseControland Preventionstressed thevalueofbloodscreeningforHBVandeventualanti-HBVvaccinationinthe prisoncommunityfor thosepersonswhounderwentamedicalassessmentinprison [20].Despite the factthatvaccination againstHBVhasbeenrecommendedinprisonssincethevaccinebecameavailablein1982, onlyafewcountriesroutinelyvaccinate inmates[21].

InOctober1991,anItalianministerialdecreeproposedHBV vaccineforpeopleat risk, including inmates. Vaccination is requiredat months0, 1, and 2 at the moment. ThereisanextendedcalendarforHBVimmunizationforpeoplewhoarehomeless (0,7,and21days)withaboosterat12 months,whichresultsinbetteradherenceand seroconversionratesthanstandard services.Inmates'failureto complywiththe screening schemeisoneofthe keyreasonsthat theyarenotvaccinated. Noncomplianceislikelydueto acombinationofpersonalandinstitutionalfactors, including a lack of information and understanding (perceived risk) about viral hepatitisand transmissionpathways,alack ofmotivationand/orawarenessofthe protocol,and a fearofstigma fromprison personneland colleagues[22].

VanHercketal.[23]noticedthatanaccelerated(0,1,2,and12month)orsuperaccelerated(0,7,21days,andafter12months)planwouldresultinafasterresponsanda10IU/Lriseinanti-hepatitisBsurface(HBs)antibodies.Forgroupsathigh riskofinfection,themostacceleratedsoftwareisneededforrapidseroconversion andimmediatedefense intheshortterm.Sincenolong-termsafetyproofforthese more accelerated programs has been published, a fourth dose permonth is still needed.

Stasietal.[24]evaluated1,075subjectsscreenedforHBV serummarkers,67.9% weresusceptibletoinfectionandneededto bevaccinated,ofthese82%agreedtobe vaccinated.Fivehundredandfifty-fiveinmates(95.1%)gotthefirstvaccinedose, and 404 (83%)undertookthe third dose atday twenty-one.

Almasioetal.[22]proposedHBVvaccinationforrefugeesinthe followinggroups: thosefromparticularlyendemiccountries, opioidaddicts,non-immunizedinmates, partnersofinfectedindividuals,and patientswithchronic liverdiseaseunrelatedto

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HBV.Alloftheseclasses,inparticular,shouldbegivenacceleratedvaccination to ensure ahighlevelofcompliance and preventdropouts.

Incomparisontostandardvaccineschedules, Wrightetal.[25]emphasizedthevalue ofanextended vaccination cycle (0,7,21 days)with aboosterat12 months for homeless subjects, which resultsin bettercompletion ratesand equivalent seroconversionrates.

The investigators argued that HBVvaccine is a cost-effectivemeasure inmany unvaccinatedhigh-riskindividuals,andthat itisasuitablecomplementtonational immunization systems. HBV vaccinewas only used in national immunization servicesin the Netherlandsin 2011.Pregnantwomen should bescannedforHBV infectionattheir firstprenatalmeeting,accordingto theUSPreventiveServicesTask Force[26].

ArecentstudybyCatherineandPiroth[27]stronglyrecommendedHBVvaccination inpeople livingwithHIV,basedoncurrently availableevidenceaboutHBVvaccinationinpeoplelivingwithHIV,accordingtotheirkeycharacteristicsandvaccineandtherapeuticcontext,inaccordancewithinternationalrecommendations onHBVvaccinationinhumanimmunodeficiencyvirus(HIV)-infectedpopulations. A seroconversionofanti-HBsantibodies>10IU/mLindicatesapositiveresponse to vaccination.InHIV-infectedpopulations,double-doserescuevaccineforatleast threedosestendsto cause improved HBVimmunization, asdoesannualanti-HBs antibody titermonitoring[28, 29].

Beyond the current therapy for chronic hepatitisBvirusinfection

TreatmentisindicatedinalladultsteenagersandchildrenwithchronicHBVinfectionandcompensatedordecompensatedcirrhosis,regardlessofhepatitisB e antigen (HBeAg)status,orHBVDNA levels,according toWHOrecommendations forHBVprevention,care,and treatment.AdultswithchronicHBVinfectionthatdo nothaveclinicalsymptomsofcirrhosisbutare over the ageof30 who have persistently elevated ALTlevelsand excessive levelsofHBVreplication (HBV DNA >20,000IU/mL),regardlessofHBeAgstatus,areadvisedtoseektreatment.Theserecommendationsarebasedonapublicpolicyperspective,andtheytookviability and efficacy into account[30].

Current antiviral agents, such as tenofovirand entecavir, have a lowchance of resistance, have a viral suppression rate of over 99 percent, and have a high tolerability rate.Severallinesofevidence indicate that long-termcomplete inhibition ofHBVreplication by nucleosides/nucleotides (NUC)leadsto better long-term outcomes, including a lowerchanceofdeveloping livercirrhosis, hepatocellular insufficiency, and hepatocellularcarcinoma[31, 32], aswellashistologically confirmed reversalofliverfibrosis. The drawbacksinclude the treatment's indefinite duration,lowrate ofHBsAgfailure, and seroconversionto anti-HBs[33].

HBVmedicationsthatcauselong-termrepressionofHBV-DNA,HBsAgnegativity,andcccDNAeradicationarealsobeingtested.Interferoncausesimmunomodulation and cccDNA transcriptionrepression,butantiviraldrugsthattargetvariousstagesoftheHBVlifecyclearenowbeingdeveloped.DrugsthattargetcccDNArebeinginvestigated,including inhibitorsofcccDNAproduction, transcription inhibitors,and drugsthatdisturbordegradecccDNA[34].Otherdrugscurrently indevelopment includeinhibitorsofvirus translocationinthecytoplasmornucleocapsidassemblyto DNA, aswellasinhibitorsofHBsAgrelease[35].

Finally, modernimmunomodulatorsare in a later stage of development. HBV- specific immunomodulators, anti-programmed celldeath protein 1, andtherapeutic vaccinesthatimprove theimmune response are amongthem[36].

Vaccinetherapy for chronic hepatitisBvirus infection

HBVpersistenceiscausedbyacomplexrelationshipbetweenthevirusand thehost,whichresults insuboptimal immuneresponsessuchascell-mediated immunity and dendritic celldysfunction, aswellascytokine synthesisimbalance[37].

In chronic HBV-infected patients, therapeutic vaccination will triggeranti-HBV immune responsesthatremove and/orcure infected hepatocyteswithoutcausing host celldamage,preventingviraldistribution to newhepatocytesandconfirming long- termviralcontrol[38].Differentvaccination dosesand frequencies, aswellasprime-boost,areusedtostimulateT-cellresponseswiththerapeuticvaccination,asare DNAorpeptidevaccines,vectororcell-basedvaccines,andfinallyamixtureof heart, X, and polymerase antigensinadditionto HBsAg[38, 39].

ThirtytwochronicHBsAgcarriersofchronichepatitisandobservableHBVDNAweregiventhreenormaldosesoftheGenHevacB vaccineatone-month intervalsin oneofthe firstclinicalstudieson HBVvaccinetherapy.Twelve patients (37.5%)had undetectableHBVDNAsixmonthsafterthefirst injection, whilethreeothershad substantialdecreasesinHBVDNA titers.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Andafteratypicalcourseof-interferon, eightofthe15 respondersalso hadundetectableHBVreplication.Thirteenofthe17 non-responderstothevaccineweregiven-interferon,butonlythreeofthemwere ableto stop HBVreplication. Finally,53%ofHBVpatientshadHBVDNAthatwasundetectable[40]Laietal.[41]recentlyvaccinated20chronicHBV compromisedeantigen-negative patientswith HBsAg 1,000 IU/mLin astudy.Sevenvaccine doses were given every eightweeks, and HBsAg and anti-HBs levels were tracked for48 weeks after vaccination.Thevaccineresulted inasubstantialreductioninHBsAginthese patients.

Bian etal.[42]looked atwhetherpreS1-polypeptide vaccine could be used to treat chronicHBVpatients.Theydiscovered thatL-preS1HBsAg'sdomainhasahigh immunogenicity forboth B-cell and T-cell responses. Furthermore, anti-preS1 inducedbypreS1-polypeptidecleared HBVDNAincarriermiceandprevented HBV infection/reinfection ofhepatocytes, implying thatsubsequentHBsAg vaccination could induceanti-HBsseroconversionin HBVcarriermice.

Zoulimetal.[43]studiedthe stability, immunogenicity, andefficacyofTG1050 in chronic HBV-infected patientsin a phase Iclinical trial. TG1050 isan adenovirus-5- basedvaccinethatcontainsHBV polymeraseaswellascentralandsurfaceantigen domains.Thereweretwostepsofthisstudy:asingledosecohortandamultiple dosescohort.Inbothcohorts,TG1050waswelltolerated,and itwascorrelatedwith an HBV-specific cellularimmune response.

Bonietal.[44]evaluatedtheeffectivenessandprotectionofGS-4774inviremicHBVcontaminated patientsin aphase IIclinical trial. Tenofovirdisoproxilfumaratewasgiventobothofthesepatients,either withorwithoutGS-4774.GS-4774isa preventivevaccine made fromyeast.GS-4774mediated interferon-producingCD4+ and CD8+Tcells in a murine modelandcells fromchronic HBV infected patients [45].

Bonietal.[44]discoveredthatvaccination wouldboosttheimmuneresponseby increasing the developmentofinterferon-, tumornecrosis factor, and interleukin 2 by CD8Tcellsexposedtoantigenicpeptides, withlittleeffectonCD4Tcells,andthat GS-4774could be used in conjunction with otherantiviraltreatmentsto boost the immuneresponse.AlMahtab etal.[46]compared the effectivenessofa preventive vaccine (NASVAC) containingbothHBsAgandhepatitisBcore antigentopegylatedinterferoninatotal of160chronicHBVinfectedpatientsina phaseIIIclinicaltrial.At24weeksof follow-up,theviralloadintheNAVASC communitywasslightlylower thaninthe pegylated interferongroup.HBeAgclearancewasalsohigherin theNASVAC group relative tothepegylated-IFNgroup,but therewasasmalldevelopment intocirrhosis in the NASVACgroup compared to the pegylated-IFNgroup.

Inapilottrial,Brillantietal.[47]randomlyallocatedfivepatients withHBeAg- negative chronicHBV infectiontoundergo HBVvaccinetherapy:threedosesof40 mcgyeastderivedrecombinanthepatitisB vaccine(HBVAXPro)givenonemonth apart,whilefivepatients receivednucleos(t)ideanalog therapyonly.Thepresenceof HBsAgandHBVDNAwasdetermined sixmonthslater.Thevaccinetherapy increased HBsAglossand anti-HBsseroconversionin the HBVAXPro community.

Conclusion

ThebestdefenseagainstchronicHBVinfectionanditscomplicationsistheHBVvaccine.RoutineHBVimmunizationofinfantsha simproved globally,withan averagecoverageof84 percent in 2017, butmore work is required in many countries to implement thiscoverageandguaranteenationalpolicies forindividualsathigh risk ofHBVinfection.Severallinesofevidence suggestthattherapeuticvaccineshave shownpromise inmurineandhumantrials, butfurthermulticenterresearch clinical testsareneeded toconfirmthesefindings.Combinationtreatmentsseem toboostthe potency oftherapeutic vaccinesthat increaseT-cell tolerance.

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