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Contemporary Practice in Paediatrics

Recommendations in the Prevention and Management of Hepatitis B Reactivation in Paediatric Patients Receiving Immunosuppressive Therapy in Hong Kong Special Administrative Region, China

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Abstract Hepatitis B reactivation can be a fatal complication of paediatric hepatitis B patients receiving immunosuppressive therapy. However, there is no specific recommendation in paediatric patient group. This article aims to summarize the paediatric recommendations from international guidelines with reference to Hong Kong SAR paediatric data. Hepatitis B reactivation risk is stratified into "high risk group", "moderate risk group" and "low risk group". All paediatric patients who will receive immunosuppressive therapy in moderate and high risk groups should be tested for hepatitis B surface antigen and antibody to hepatitis B core antigen prior to receiving treatment. Hepatitis B deoxyribonucleic acid (HBV DNA) level should be checked if the patients' either test is positive. Antiviral prophylaxis should be given in high risk group patients. Antiviral prophylaxis should be considered in moderate risk group patients. Hepatitis B screening tests and antiviral prophylaxis are not recommended in low risk group. Entecavir and Tenofovir disoproxil fumarate are drugs of choice.

Key words *HBV reactivation; Immunosuppressive therapy; Paediatric*

Introduction

As medicine advances, more intensive or wider indications of immunosuppressive therapy are now offered to various paediatric patients (e.g. high dose corticosteroids; intensive systemic chemotherapy for haematological malignancies and solid tumours; potent immunosuppressive or immunomodulating therapy including biologics for refractory autoimmune diseases).

In Hong Kong, hepatitis B virus (HBV) infection is still endemic in the overall population. It is expected that the risk of HBV reactivation in paediatric patients receiving immunosuppressive treatment and with prior HBV infection will be significant. The consequence of such hepatitis flare may be fatal. On the other hand, Hong Kong has commenced universal HBV vaccination program since 1988. The vaccine coverage rate is over 99%.[1] Hence, the majority of local born mothers of child bearing age under the age of 30 had received HBV vaccine.

However, there is still mother-to-child transmission (MTCT) despite very effective universal vaccination program and post-natal immunoprophylaxis with HBV immune globulin (HBIG) in babies born from hepatitis B surface antigen positive (HBsAg+) mothers.[2] These MTCT transmitted cases together with postnatal acquired cases will thus be subjected to the potential risk of HBV reactivation during their immunosuppressive therapy.

The Coordinating Committee (COC) (Paediatrics) under Hong Kong Hospital Authority (HA) endorsed this recommendation. This recommendation is produced by the Working Group (WG) of prevention and management of hepatitis B reactivation in paediatric patients receiving immunosuppressive therapy in Hong Kong SAR. The WG was launched and formed by COC (Paediatrics) under Hong Kong HA.

Rationales for a Different Paediatric Guideline for Paediatric Patients Undergoing Immunosuppressive Therapy

There is number of reasons to set up a paediatric guideline in this special patient group: (1) paediatric population has much lower HBsAg+; and HBsAg negative and antibody to hepatitis B core antigen positive (HBsAg–/anti-HBc+) prevalence; (2) some diseases only occur in children like neuroblastoma and retinoblastoma while others are more common in paediatric population such as minimal change glomerulonephritis, acute leukaemia, brain tumour or lymphoma; (3) the treatment response in paediatric patients to the therapy is different. Treatment success rate of haematologic malignancies such as acute leukaemia and lymphoma are better in paediatric population; (4) there is significant differences in treatment regimen – intensity of chemotherapy for haematologic and solid tumour malignancies is usually much higher resulting in more profound immunosuppression; and (5) the recommended dose used in paediatric patients is based on body weight or body surface area.

HBV Serology Status in Paediatric Population

The presence of anti-HBc indicates past history of or resolved HBV infection with or without HBsAg and antibody to HBsAg (anti-HBs) positivity. Knowledge of the patient's anti-HBc status is useful as HBV reactivation can happen if the patient undergoes immunosuppressive treatment even when HBsAg is negative.

The exact prevalence of anti-HBc in Hong Kong population is not known. In East Asia region, it is estimated the anti-HBc+ prevalence is ranging from 13.5% to 40.9%

in adult population.[3-5]

Since there is no local paediatric seroprevalence data on HBsAg and anti-HBc status, the WG estimated (1) the HBsAg+; and (2) HBsAg–/anti-HBc+ paediatric seroprevalence from local MTCT data.[6] In this 30-year cohort study in Hong Kong, the MTCT rate was 3.5% among HBsAg+ mothers and the majority of MTCT occurred before age of 2.[6] As the latest overall expectant mothers' HBsAg+ prevalence is around 5%,[1] the estimated paediatric HBsAg+ prevalence is estimated to be about 0.17% at age of 2 due to MTCT. The prevalence is expected to increase after adolescent age because of subsequent horizontal transmission, notably from sexual contact. The data shows that HBsAg+ prevalence is around 1% which is the prevalence in expectant mothers with age less than 20.[1]

In the same 30-year cohort study, anti-HBc seroconversion rate with HBsAg– status in children born from HBsAg+ mothers was 9%. Around half of anti-HBc seroconversion occurred before age of 2 while the other half occurred over the next 20 years.[6] Therefore, the HBsAg–/anti-HBc+ prevalence in general paediatric population is estimated to be 0.45% in toddler age and up to 0.8% in early adulthood. Nearby regions with similar HBV prevalence has reported HBsAg–/anti-HBc+ paediatric prevalence up to 2.4%.[7]

Caseload Estimation on Paediatric Patients Requiring Immunosuppressive Therapy with Prior HBV Infection

Searching the Clinical Data Analysis and Reporting System (CDARS) for all paediatric patients under the HA service and have used various immunosuppressive therapy over 2 years period from 1st April 2015 to 31st March 2017, there are total 2081 patients retrieved, i.e. 1040 patients receiving immunosuppressive therapy each year.

This number correlates well with the summation of estimated number of new cases requiring immunosuppressive therapy (around 1000 per year) from various subspecialties (oncology, nephrology, rheumatology, gastroenterology and hepatology, respirology, infectious diseases, cardiology, neurology and endocrinology).

As the estimated local paediatric HBsAg+ prevalence ranges from 0.17% to 1% and HBsAg–/anti-HBc+ prevalence ranges from 0.45% to 2.4%, it is expected the annual number of paediatric patients requiring immunosuppressive therapy with HBsAg+ or anti-HBc+ is about 1000x(1%+2.4%)=34.

Immunosuppressive Therapy with Profound or Significant Immunosuppression

The most significant therapy that can cause profound immunosuppression is B-cell depleting agents, e.g. rituximab and afatumumab; B-cell and T-cell depleting agent, e.g. alemtuzumab; and haematopoietic stem cell transplant (HSCT) therapy.

The less profound but still very significant immunosuppression is systemic chemotherapy (e.g. oncologic or nephrology conditions). The systemic chemotherapy include alkylating agents (e.g. cyclophosphamide, ifosphamide, temozolamide, cisplatin, carboplatin); plant alkaloids (e.g. vincristine, vinblastine); anti-tumour antibiotics (e.g. doxorubicin, daunorubicin, idarubicin, actinomycin, bleomycin); antimetabolites (e.g. methotrexate, cytarabine, fludarabine, clofarabine); topoisomerase inhibitor (e.g. irinotecan, topotecan, etoposide); and enzymes such as asparaginase.

Other immunosuppressive therapy can cause significant immunosuppression include moderate to high dose corticosteroids, tumour necrosis factor (TNF) alpha inhibitor (e.g. etanercept, adalimumab, certolizumab, infliximab, golimumab), cytokine or integrin inhibitor (e.g. abatacept, ustekinumab, natalizumab, vedolizumab), tyrosine kinase inhibitors (e.g. imatinib, nilotinib), and others immunosuppressive agents (e.g. mycophenolate mefotil (MMF), 6-thioguanine, cyclosporine, tacrolimus, sirolimus etc.).

Traditional immunosuppressive agents include azathioprine, 6-mercaptopurine and methotrexate monotherapy cause less immunosuppression as compared with the above agents and therapy.[8]

Paediatric Systemic Corticosteroid Dosing for Risk Stratification

The exact dosing for low, moderate or high dose and duration of corticosteroids that can cause substantial immunosuppression is uncertain. Advisory Committee of Immunization Practices (ACIP)[9] and American Academy of Pediatrics (AAP)[10] recommend 20 mg or more prednisolone daily or equivalent for longer than 2 weeks is generally considered clinically significant to induce immunosuppression.[11] A recent report shows that high

dose (more than 40 mg daily) corticosteroid less than 7 days can cause significant hepatitis flare in HBsAg+ adult patients.[12] Therefore, the WG categorises steroid dosing into (a) low dose and (b) moderate to high dose group. The duration of significant exposure is beyond 2 weeks.

a. Low Dose Steroid Group:

i. Any doses of systemic corticosteroid given daily or on alternate day for less than 2 weeks.
ii. Topical therapy, local injection, intra-articular or aerosol use of corticosteroids, or physiological maintenance doses of corticosteroids.

b. Moderate to High Dose Steroid Group:

i. Moderate or high doses of systemic corticosteroids given daily or on alternate day beyond 2 weeks.
ii. Steroid dosing: receiving ≧ 1 mg/kg per day up to ≧ 40 mg per day (irrespective of body weight) of prednisolone or its equivalent, or ≧ 10 mg/day if they weigh more than 10 kg.

Risk of HBV Reactivation

The risk stratification is based on the anticipated incidence of reactivation reported from literatures. In general, the risk would be related to the premorbid HBV status and the degree of immunosuppression (treatment risk). The following combined risk stratification may not be comprehensive. Clinical judgement is required, especially when patients are given combination of multiple immunosuppressive therapies.[13]

a. High Risk Group (Anticipated Incidence of Reactivation >10%)

i. HBsAg+ or HBsAg–/anti-HBc+ patients treated with B cell-depleting agents, B-cell and T-cell depleting agents or HSCT recipient;
ii. HBsAg+ patients treated with systemic chemotherapy for oncologic conditions;
iii. HBsAg+ patients treated with ≧1 mg/kg per day up to ≧40 mg per day (irrespective of body weight) of prednisolone or its equivalent, or ≧ 10 mg/day if they weigh more than 10 kg, of systemic corticosteroids given daily or on alternate day beyond 2 weeks.[9-11]
iv. HBsAg+ patients treated with anti-rheumatic therapy such as anti-TNF agents or disease modifying anti-rheumatic drugs (DMARDs).[14]

b. Moderate Risk Group (Anticipated Incidence of Reactivation 1-10%)

i. HBsAg–/anti-HBc+ patients treated with systemic chemotherapy for oncologic conditions;
ii. HBsAg–/anti-HBc+ patients treated with TNF alpha inhibitors, cytokine or integrin inhibitors, tyrosine kinase inhibitors or DMARDs;
iii. HBsAg–/anti-HBc+ patients treated with ≧1 mg/kg per day up to ≧ 40 mg per day (irrespective of body weight) of prednisolone or its equivalent, or ≧ 10 mg/day if they weigh more than 10 kg, of systemic corticosteroids given daily or on alternate day beyond 2 weeks.[9-11]

c. Low Risk Group (Anticipated Incidence of Reactivation < 1%)

i. HBsAg+ or HBsAg–/anti-HBc+ patients treated with traditional immunosuppressive agents monotherapy, e.g. azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX);
ii. HBsAg+ or HBsAg–/anti-HBc+ patients treated with any doses of systemic corticosteroid given daily or on alternate day for less than 2 weeks;
iii. HBsAg+ or HBsAg–/anti-HBc+ patients receiving topical corticosteroid therapy;
iv. Local injection, intra-articular or aerosol use of corticosteroids, or physiological maintenance doses of corticosteroids.

In patients receive low dose corticosteroid or traditional immunosuppressive monotherapy, if their conditions deteriorate and immunosuppressive therapy need to be stepped up or changed to combination immunosuppressive therapy, these patients' risk of HBV reactivation will increase to moderate or high risk according to patients' HBV status. Therefore, HBsAg and anti-HBc should be checked during screening. In new immunosuppressive therapy with an uncertain risk of HBV reactivation, it is suggested to manage these patients as moderate to high risk group according HBV status.

Proposal on HBV Infection Screening Strategy in Patients Receiving Immunosuppressive Therapy

There is no need to check HBsAg and anti-HBc in low treatment risk group for HBV reactivation such as using short term, low dose or physiological systemic corticosteroid therapy; topical, or local corticosteroid therapy. Though some traditional immunosuppressive agent monotherapy e.g. AZA, 6-MP alone have low treatment risk of HBV reactivation, these patients may have underlying condition which may subsequently deteriorate and need to step up of immunosuppressive therapy with higher treatment risk. Therefore, HBsAg and anti-HBc

should also be checked during screening in patients requiring single traditional immunosuppressive agent if potential escalation of immunosuppression therapy is anticipated.

All paediatric patients who will receive immunosuppressive therapy in moderate and high treatment risk groups for HBV reactivation should be tested for HBsAg **and** anti-HBc prior to receive treatment as there is a significant risk of HBV reactivation in HBsAg+ or HBsAg–/anti-HBc+ patients.[15]

If a patient is found to be HBsAg+ or anti-HBc+, HBV deoxyribonucleic acid (DNA) level should be checked. For HBsAg–/anti-HBc+ patients with detectable HBV DNA level, the risk of HBV reactivation is similar as in HBsAg+ patients and their management should be the same.[16,17]

There is no role in using anti-HBs to detect HBV reactivation. Individual consideration can be made on the need of HBV revaccination in those found to be non-immune (both anti-HBs negative and anti-HBc negative, anti-HBs–/anti-HBc–), especially in those patients with ongoing exposure to blood products and risk of HBV exposure.

Laboratory test for HBsAg may be positive within 1 month after HBV vaccination. Anti-HBc result may be affected by recent blood or blood products transfusions as the prevalence of anti-HBc can be high in local adult population. The interpretation of serology results thus needs to be correlated with any recent HBV vaccination and blood products transfusion. Anti-HBc should be repeated 1 month later if required.

If HBV is not the cause for liver derangement in patients receiving immunosuppressive therapy, investigation for other hepatitis should be performed including hepatitis A (HAV), hepatitis C (HCV), hepatitis E (HEV) and or even rat HEV if HEV immunoglobulin (IgM) positive but HEV nucleic acid not detected.[18]

Definition of HBV Reactivation and Hepatitis Flare

The American Association for the Study of Liver Diseases (AASLD) recommended using evidence of HBV reactivation AND a hepatitis flare to define HBV-associated hepatitis.[15]

The Definition of HBV Reactivation is as Follows:

HBsAg+ patients:

1. ≧2 log (100-fold) increase in HBV DNA compared to the baseline level,
2. HBV DNA ≧ 3 log (1,000) IU/ml in a patient with previous undetectable level (since HBV DNA levels fluctuate), or
3. HBV DNA ≧4 log (10,000) IU/ml if the baseline level is not available

HBsAg–/anti-HBc+ patients:

1. HBV DNA is detectable OR
2. HBsAg seroreversion occurs (reappearance of HBsAg)

The definition of hepatitis flare is an alanine aminotransferase (ALT) increase to ≧3 times from baseline AND >100 U/L.

Clinical Recommendations on the Use of Antiviral Prophylaxis[13]

High Combined Patient and Treatment Risk Group

The consensus of WG supports antiviral prophylaxis over no prophylaxis for high risk group as the risk of HBV reactivations in these patients receiving anti-cancer or anti-rheumatic therapy is high.

Moderate Combined Patient and Treatment Risk Group

It is recommended to consider starting antiviral prophylaxis. For patients and or families who do not want starting long term antiviral therapy, serial monitoring of liver function test (LFT) and HBV DNA during immunosuppressive therapy should be done. For those HBsAg–/anti-HBc+ patients, monitor HBsAg to look for HBsAg seroreversion. The frequency of monitoring can range from 1 to 3 months depending on the type of immunosuppressive therapy. Antiviral therapy should be initiated upon confirmation of HBV reactivation before ALT elevation.

Low Combined Patient and Treatment Risk Group

The consensus of WG does not support use of antiviral prophylaxis or preemptive therapy in low risk group patients as the HBV reactivation risk is low.

Choice of Antiviral Medications

Both entecavir (ETV) and tenofovir can be used as special drug under the current Hospital Authority Drug Formulary (HADF).[19]

ETV is the drug of choice because of its high potency and high barrier to resistance (resistance rate is 1.2% in 6 years).[17] ETV is approved by United States Food and Drug Administration (US FDA) for treatment of chronic HBV

infection in paediatric patients with age ≥2 years of age. The dosage is according to body weight (Appendix 1).

Tenofovir disoproxil fumarate (TDF) is also of high potency with even lower resistance rate as compared with ETV as evidenced by no resistance development after up to seven years of TDF use.[17] However, renal function and serum phosphate level should be closely monitored as TDF has small risk of inducing proximal tubular dysfunction and renal insufficiency during treatment. US FDA has approved paediatric use for treatment of HBV infection in age >12 years with body weight >35 kg (Appendix 1).

Newer generation tenofovir alafenamide (TAF) has the benefit that lower dose of tenofovir can be used with similar efficacy and with much lower proximal tubule dysfunction and renal insufficiency side effects. However, TAF is not yet approved by US FDA for the treatment of HBV infection in the paediatric age group.

Both ETV and TDF need renal adjustment of dosage in patients with renal impairment (creatinine clearance less than 50 ml/minute) (Appendix 2).

Treatment Monitoring and Duration[15-17,20-22]

Antiviral prophylaxis should be started as soon as possible and at least 1 week before or at the initiation of immunosuppressive therapy if feasible. It should be continued for at least 6 months after discontinuation of such therapy and at least 12 months after B cell depleting agents or HSCT. In emergency corticosteroid treatment, urgent HBsAg and anti-HBc should be checked and corticosteroid treatment should not be delayed till HBsAg and anti-HBc results are available.

If there is any uncertainty towards the clinical need of long-term antiviral therapy, it is advisable to refer these patients to specialists such as paediatric hepatologists, or paediatric infectious diseases specialists for further management.

While on antiviral prophylaxis therapy, initially LFT should be monitored every 3 months, or more frequent as clinically indicated. If TDF is used, renal function test (RFT) and serum phosphate should be monitored at the same time frame as LFT. Serum HBV DNA should be monitored every 3 to 6 months while on antiviral therapy. Patients and families should be reminded of the risk of HBV reactivation and hepatitis flare after discontinuation of antiviral prophylaxis.

For HBsAg+ patients after antiviral prophylaxis therapy discontinuation, LFT should be monitored at 1 and 3 months and then every 2 to 3 months. HBV DNA should be checked at 1 and 3 months after discontinuation of antiviral prophylaxis therapy. For patients treated with B cell depleting agents and HSCT recipients, HBV DNA should be checked at 1, 3 and 6 months after discontinuation of antiviral prophylaxis. Antiviral therapy should be promptly resumed if evidence of HBV reactivation and patients can be referred to specialists for assessment.

For those moderate combined patient and treatment risk group patients who opt for no antiviral prophylaxis therapy, the frequency of monitoring of HBV DNA can range from 1 to 3 months depends on type of immunosuppressive therapy. Antiviral therapy should be initiated upon confirmation of HBV reactivation.

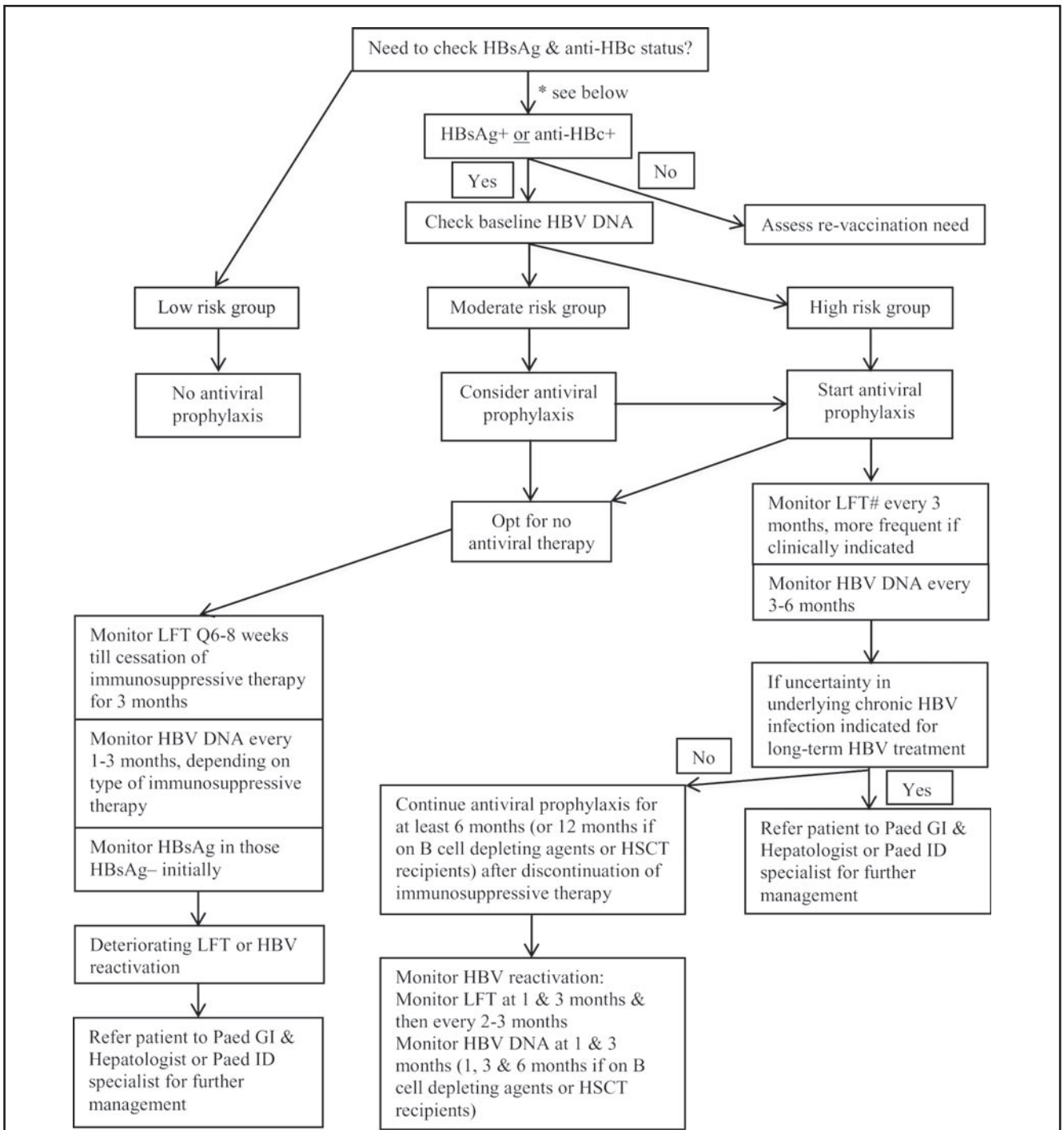
For HBsAg–/anti-HBc+ patients, HBsAg and LFT should be checked to look for HBsAg seroreversion, i.e. HBsAg reappearance. HBV DNA then should be checked when HBsAg turned positive or ALT goes up. The frequency of monitoring can range from 1 to 3 months depending on the type of immunosuppressive therapy. Antiviral therapy should be initiated upon confirmation of HBV reactivation.

Special Patient Group – Non-liver Solid Organ Transplant Recipients[15-17]

The WG determined that paediatric liver transplant recipients' management is beyond the scope of this recommendation. The management of liver transplant recipients' HBV reactivation should be referred to the liver transplant center's practice guideline in Hong Kong.

The majority of non-liver solid organ transplant patients are renal transplant in Hong Kong. These patients require dialysis and are at risk of ongoing HBV infection due to frequent blood products exposure and they have impaired immune response to HBV vaccine before transplantation. It is suggested that they should be evaluated for HBV infection and immunity annually, i.e. HBsAg, anti-HBc and anti-HBs. HBsAg–, anti-HBc–and anti-HBs–recipients should receive HBV re-vaccination pre-transplant if HBsAg–. Organ transplant recipients with HBsAg+ should receive lifelong antiviral therapy to prevent or treat HBV reactivation after transplantation. ETV and TDF are the preferred antiviral drugs.

It is suggested to monitor HBV reactivation without antiviral prophylaxis in HBsAg–/anti-HBc+ patients, or consider treating these patients with antiviral therapy for the first 6 to 12 months during the maximal immunosuppression. It is recommended to monitor HBV reactivation by checking HBsAg (HBsAg seroreversion), ALT and HBV DNA every 3 months or more frequently for the first year post-transplant and after receipt of T-cell-



* No need to screen HBsAg and anti-HBc in low premorbid patient risk group (e.g. short term systemic or physiological dose corticosteroid, topical or local corticosteroid therapy) **except** traditional immunosuppressive monotherapy e.g. AZA, 6-MP, MTX.
^ HBsAg and anti-HBc screening should **only** be done in low risk group patients who have **potential** to escalate immunosuppressive/corticosteroid therapy in future. Anti-HBs has no role in routine screening in all risk groups.
# Monitor RFT & PO4 if TDF is used, at the same time with LFT.

Figure 1 Algorithm of prophylactic use of antiviral therapy for paediatric patients planned for immunosuppressive/corticosteroid therapy

depleting therapies e.g. anti-thymocyte globulin during maximal immunosuppression in untreated non-liver organ transplant recipients. Antiviral therapy should be started immediately if HBV reactivation.

Declaration of Interest

Wai Hung CHAN, Mike Yat Wah KWAN, David Christopher LUNG, Winnie Kwai Yu CHAN, Mei Ching CHAN, Frankie Wai Tsoi CHENG, Chung Mo CHOW, Assunta Chi Hang HO, Tak Loi KU, Wai Ming LAI, Daniel Wai Yau MAK, Chi Hang NG, Freddie Man Hong POON, Shirley Man Yee WONG, Rosanna Ming Sum WONG, Sik Nin WONG, Eric Kin Cheong YAU, Mei-Hwei CHANG, Jia-Feng WU, Xinbao XIE, Yu Lung LAU, Kwok Chiu CHAN: None to declare

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Appendix 1. Recommended antiviral therapy for paediatric patients

1. Entecavir (ETV)

Recommended dosage in adult patients:
Treatment-naïve patients: ETV 0.5 mg daily
Lamivudine-experienced patients: ETV 1 mg daily

Recommended dosage in paediatric patients:

The following table describes the recommended dose of ETV for paediatric patients 2 years of age or older and weighing at least 10 kg. The tablet dissolves in plain water should be used for patients with body weight up to 30 kg. The current ETV formulations in HA are dispersible tablet or plain tablet. Both are readily soluble in water and dosage can be given according to body weight.

Dosing schedule for paediatric patients

	Recommended Once-Daily Dose (mg)	
Body Weight (kg)	**Treatment-Naïve Patients**	**Lamivudine-Experienced Patients**
10 to 11	0.15	0.3
>11 to 14	0.2	0.4
>4 to 17	0.25	0.5
>17 to 20	0.3	0.6
>20 to 23	0.35	0.7
>23 to 26	0.4	0.8
>26 to 30	0.45	0.9
>30	0.5	1

2. Tenofovir disoproxil fumarate (TDF)

Recommended dosage for age 12 years or older with body weight more than 35 kg:
Dosage: TDF 300 mg daily

3. Tenofovir alafenamide (TAF)

Recommended for adult only and not recommended for use if creatinine clearance less than 15 ml/minute
Dosage: TAF 25 mg daily

NB: Pharmaceutical companies do not update US FDA age limit approval in local drug insert, the WG suggested paediatricians should follow the most update US FDA approval.
US FDA approved TDF use in age from >2 years and beyond, however, TDF powder is not available in Hong Kong and hence, body weight based paediatric dosing is not included.

Appendix 2. Recommended dosage adjustment of antiviral therapy in renal impairment

Dosing schedule for paediatric patients

Creatinine clearance (ml/minute)	**Entecavir (Dose according to BW)**	**Tenofovir disoproxil fumarate (300 mg for ≧ 12 y.o. & ≧ 35 kg)**
≧ 50	Daily	Daily
30 - 49	Q48H	Q48H
20 - 29	Q72H	Q72H
10 - 19	Q72H	Q96H
<10	Once weekly	Once weekly
CAPD	Once weekly	Once weekly
Haemodialysis (Administer after HD)	Once weekly	Once weekly