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### The Cover Shot

**Bench**

This photo was taken in Stanley Park in Vancouver, Canada. By the breezy sea, there sits a bench with a plaque that reads, ‘Look to the sea, and thy heart shall soar.’ – remembering a loving husband and father who loved the sea. Now that he has passed away, he can be with the sea forever.

When we look back, there are always regrets: we could have appreciated the happy times we spent with our loved ones longer; we could have worked harder; we could have been to more amazing places. When we look forward, there are always goals, plans and dreams we want to achieve. Few people appreciate the present and take the time to feel the very moment. *Carpe diem* – It is important that we seize the day and cherish every present moment, to feel, to appreciate, to soar.

---

**Mr Kai-man HO**

Advance Practice Nurse,  
Princess Margaret Hospital  
Fellow of the HK Academy of Nursing in Infectious Disease

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![Image of people with an arrow pointing down 90%](image)

**Men Who Have Sex with Men (MSM)**

![Image of people with an arrow pointing down 92%](image)

in TRUVADA users with detectable drug levels in plasma or peripheral-blood mononuclear cells vs those without detectable drug.

**Health Guidelines Recommend TRUVADA for PrEP**

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- World Health Organization
- International Antiviral Society-USA
- The American College of Obstetricians and Gynecologists

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**Presentation:** Blue, capsule-shaped, film-coated tablet, debossed with “GILEAD” on one side and with “701” on the other side. Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate.

**Blue, capsule-shaped, film-coated tablet, debossed with “GILEAD” on one side and with “701” on the other side. Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate.**

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**Dosage:** One tablet, once daily, either with or without food.

**Side Effects:** The most common adverse reactions reported in randomized clinical trials of adults were nausea, diarrhea, headache, fatigue, and respiratory tract infection. In clinical trials, headache was the most frequent adverse reaction reported in the iPrEx study was headache. Please refer to full prescribing information for full list of adverse reactions.

**Pre-exposure prophylaxis:** No new adverse reactions to TRUVADA were identified. The most frequent adverse reaction reported in the Truvada for HIV prevention study was headache. Please refer to full prescribing information for full list of adverse reactions.

**Precautions:** Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

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**References:**


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When I got invited to be the guest editor for this issue last year, I decided to focus on viral diseases as this is an area where there are ever-changing developments in diagnosis and management and also vast public health implications. It was last year that I chose to dedicate the theme for this issue to be on ‘Viral diseases of global importance’ and started to approach authors. Little did I know that the COVID-19 would emerge as a pandemic with unprecedented devastation globally just a few months later!

In this issue, we are excited that Dr Jacky Chan and Dr Owen Tsang have kindly shared their precious experience and perspectives on COVID-19 therapies amid their extremely busy schedule while fighting with COVID-19 at the most front line. They have put in huge efforts in summarising the state-of-the-art management options for COVID-19.

Viral hepatitis B and C are two other viruses associated with significant morbidity and mortality. To this end, the World Health Assembly in 2016 adopted Global health sector strategy on viral hepatitis, 2016-2021, which outlined a global goal of eliminating viral hepatitis as a major public health threat by 2030. The Centre for Health Protection has set up a Viral Hepatitis Control Office to formulate local strategies and an action plan. A Steering Committee on Prevention and Control of Viral Hepatitis was set up. Dr Rebecca Lam, the Consultant in charge of the Office, details the comprehensive local action plan and its implementation in the article ‘Elimination of Hepatitis B and C in Hong Kong’. Focusing on mother-to-child-transmission of hepatitis B, an antiviral Tenofovir has been recommended to be added to existing hepatitis B vaccine and immunoglobulin program to further reduce the transmission rate from hepatitis B carrier mothers to their babies. Dr Wing-cheong Leung will explain the rationale behind and its implementation in Hong Kong in the article entitled ‘Use of Tenofovir in further prevention of mother-to-child-transmission (MTCT) of hepatitis B virus (HBV)’.

Apart from hepatitis B and C viruses, human papillomavirus (HPV) infection is another important yet largely ignored virus with high cancer-causing potential at various anogenital and oropharyngeal sites. It is the commonest sexually transmitted diseases and is acquired very soon after sexual debut. Although HPV vaccine is useful in preventing the infection, the exposed and unvaccinated population are prone to the carcinogenic sequelae of HPV infection. Anal cancer is on the increasing trend worldwide in the past three decades. It is actually more common in women than men, especially in women with previous genital HPV infection or precancer/ cancer. People who are infected with HIV, another important pandemic virus of the last century, HPV behaves more aggressively, and the risk of AIDS is at least 30 times more than the general population! In the article ‘High Resolution Anoccopy for the management of HPV-associated Anal Intraepithelial Neoplasia’, I shall explain the rationale for screening in high-risk populations and on the use of HRA.

For the lifestyle section, originally I have invited my friend from the UK, who is a doctor, to share his wisdom on ways to enhance resilience among healthcare workers in the context of high work stress and burnout rate. Unfortunately, my friend came down with COVID-19 and had to take time for rest for a full recovery. He would be pleased to share with us in another issue when the opportunity arises. In the urge of time, I have decided to share one of my hobbies, sound therapy, and written an article in collaboration with one of my teachers and friends, Anthony Nec from the UK. Dr Andrew Tin-yau WONG

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Editor
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References:
Elimination of Hepatitis B and C in Hong Kong

Dr Rebecca Kit-yi LAM
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INTRODUCTION

In recognition of the growing burden of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and the advances in the prevention and treatment of chronic hepatitis, the World Health Assembly in 2016 adopted Global health sector strategy on viral hepatitis, 2016-2021, which outlined a global goal of eliminating viral hepatitis as a major public health threat by 2030. The strategy provides a set of global targets, covering both impact (incidence and mortality) and service coverage. The impact targets refer to achieving a reduction of 90% in incidence and 65% in mortality by 2030, as compared with the baseline figures in 2015. Service coverage targets cover key interventions on (i) hepatitis B vaccination, (ii) prevention of mother-to-child transmission of HBV, (iii) harm reduction, (iv) blood safety, (v) injection safety, (vi) diagnosis of viral hepatitis B and C, and (vii) treatment of viral hepatitis B and C.

The Government of Hong Kong Special Administrative Region is determined to meet the World Health Organization (WHO) targets. It announced in the 2017 Policy Address the setting up of a steering committee to formulate strategies to prevent and control viral hepatitis effectively. Co-chaired by the Director of Health and the Chief Executive of the Hospital Authority, the Steering Committee on Prevention and Control of Viral Hepatitis (SCVH) was established in July 2018. The SCVH has been tasked to review local and international trends and developments in the prevention and control of viral hepatitis; advise the Government on policies and cost-effective targeted strategies for prevention and control of viral hepatitis; as well as conduct and coordinate the surveillance and evaluation of viral hepatitis control and recommend an appropriate response.

Against this background, this article discusses viral hepatitis elimination strategies for progressing towards the 2030 WHO targets in our local context in Hong Kong. As there are considerable differences in the epidemiology and interventions, strategies for eliminating new cases and deaths attributable to HBV and HCV infections would be elaborated respectively.

OVERALL STRATEGIES

Seroprevalence of hepatitis B surface antigen (HBsAg) has been decreasing in many populations without apparent risk of infection, such as new blood donors, antenatal women and pre-marital/pre-pregnancy screening clients, suggesting a shift from a region of high-intermediate to intermediate-low hepatitis B endemicity in the past decades. However, the age- and sex-adjusted prevalence of HBsAg in the latest territory-wide epidemiological study remained high at 7.2%, implying that over 500,000 people were having chronic hepatitis B in Hong Kong. The major burden of HBV infections lies in the adult population (aged 30 or above) who did not benefit from the universal neonatal hepatitis B immunisation programme which started in 1988. Given a large size of the local general population affected by hepatitis B, the strategy shall focus on enhanced prevention of mother-to-child transmission (MTCT) and expansion of services for appropriate medical management to reduce risk of chronic liver disease.

In contrast, the prevalence of chronic HCV infection was low at 0.3% in the general population in Hong Kong, but it prevails in some specific populations. The complexity of HCV epidemiology would be best addressed by applying targeted interventions towards “micro-elimination” in the populations most affected by and at risk of hepatitis C. Micro-elimination is considered a pragmatic approach for achieving HCV elimination by breaking down national elimination goals into smaller goals for individual population segments and delivering treatment and prevention interventions using targeted methods for the sub-population segments. Pursuing the micro-elimination of HCV means working to achieve the WHO targets in specific sub-populations.

ELIMINATION OF INCIDENT CHRONIC HBV INFECTION

The risk of chronicity following acute HBV infection can be as high as 80% - 90% in infected neonates and around 30% in infected children before six years of age, in contrast to ≤ 5% in healthy adults. Knowingly, the incidence of chronic HBV infection in Hong Kong is largely driven by the infections acquired in infancy through perinatal or early childhood exposure to HBV. The primary intervention for preventing HBV infection is vaccination, which is able to induce protective antibody titres in more than 95% of healthy vaccinees.

In Hong Kong, universal hepatitis B immunisation for newborn infants and administration of hepatitis B immunoglobulin (HBIG) to those born to HBsAg-
positive mothers have been in place since 1988, in addition to routine HBsAg screening for pregnant women. A series of immunisation coverage surveys since 2001 showed that the coverage of the third dose of hepatitis B vaccine among children aged 3 - 5 was consistently reaching 99% or more, far above the 2030 WHO target at 90%. With those efforts, a significant achievement in the prevention of HBV vertical transmission was made. Hong Kong was verified by Western Pacific Regional Office of the WHO as having successfully achieved the goal of HBV control in July 2011, and was also verified as of June 2013 as having met the goal of achieving a seroprevalence of less than 1%. Despite the success, there is a residual risk of HBV transmission to the newborns. A recent local study found that MTCT has continued to occur at a rate of 1.1% (7 out of 641) and babies born to women with high viral load were particularly vulnerable.

Greater efforts should be made to further prevent MTCT given the advent of potent antiviral drugs in pregnancy category B. In fact, antiviral treatment is recommended for women with HBV DNA levels exceeding 200,000 IU per millilitre in the latest international guidelines. An initiative of providing HBsAg-positive mothers with high viral load with a treatment option to use tenofovir has been implemented in Hong Kong in a phased approach. The pilot phase commenced in two hospitals at the beginning of 2020, before rolling out in all birthing hospitals in Hospital Authority (HA).

In addition, WHO Western Pacific Region emphasises that post-vaccination serologic testing (PVST) of infants born to HBsAg-positive mothers is important to determine the effectiveness of prevention of MTCT of HBV when antenatal HBV screening is in place. The PVST shall consist of tests for both HBsAg and hepatitis B surface antibody (anti-HBs) and the result can identify infants who do not have an adequate immune response to an initial hepatitis B vaccine series as well as those infected with HBV. From experience in some provinces in China, PVST programme was demonstrated to be feasible and considered an essential strategy to ensure full protection for vaccine non-responders and appropriate medical care for those infected. Notably, various barriers, such as lost to follow up, parents’ refusal to venous blood draws and highly skilled procedure for paediatric blood sampling, have to be tackled for successful implementation of PVST.

**ELIMINATION OF HBV-RELATED DEATHS**

Testing and treatment are the primary means of reducing HBV-related deaths for the WHO 2030 targets. In spite of widely available and accessible serological and molecular tests for hepatitis B and effective antiviral treatments, the diagnosis and treatment coverage rate in Hong Kong were still far below the WHO 2030 targets at 90% and 80% respectively. Nearly 50% of the HBsAg-positive participants in a population-based study in 2015-16 were not aware of their infection status. A modelling study gave a much lower diagnosis rate for HBV infection at 27% in 2016, while an estimated 22% of those eligible for HBV treatment were being treated.

The complexities and healthcare resources required for maintaining HBV treatment for a huge number of cases in Hong Kong pose a major challenge in improving the coverage of diagnosis and treatment. Although the incidence of cirrhosis, hepatocellular carcinoma (HCC) and even death can be effectively reduced with antiviral treatments, the infection can rarely be cured, and most cases would require lifelong treatment once initiated. Regular assessments of the liver function, testing for various HBV biomarkers and surveillance for HCC are also recommended for those on antiviral treatment. Understandably, there would be substantial resource implications on drug, laboratory capacity, clinical equipment and workforce, calling for the development of alternative service model and stepwise capacity building for hepatitis B medical care.

**ELIMINATION OF INCIDENT HCV INFECTION**

As percutaneous exposure to contaminated blood is the primary cause of most HCV infection, protection of injection and blood safety are key interventions in the healthcare setting. In Hong Kong, there are guidelines and training on standard infection control practices to prevent blood-borne infections in the healthcare setting. Standard management regarding the most important blood-borne infections, including HCV, is also in place. The facility-level injection safety is protected by the standard practice of using single-use of disposable injection equipment for all therapeutic injections in healthcare facilities.

The transmission of HCV to hemodialysis patients has declined over the years due to better screening of blood products, improved dialysis procedures, and less need for blood transfusion with the availability of erythropoiesis-stimulating agents. Still, HCV prevalence remains far higher in people receiving hemodialysis than in the general population. In the HA, the prevalence of HCV infection in hemodialysis patients is around 1 - 2%. Therefore, there is an ongoing plan to treat all HCV infection of patients with end-stage renal failure undergoing dialysis (both haemodialysis and peritoneal dialysis) in the HA, irrespective of their liver fibrosis stage or candidacy for a kidney transplant.

Similar to the situation in other high-income regions of the world, injecting drug use is the major source of incidental HCV infection in the community. Recent studies gave a high prevalence of anti-HCV in people who inject drugs (PWID) and ex-PWID at 76.4% and 73.4% respectively. A Cochrane review and meta-analysis found that a lower risk of hepatitis C acquisition was associated with opioid substitution therapy (OST), which could further be strengthened with safer injection practices. It is anticipated that the methadone treatment programme, as an OST for harm reduction in Hong Kong since the 1970s, would play a role in the elimination of HCV infections among PWID. The importance of coordinated, multi-disciplinary care teams in increasing linkage of HCV care and uptake of treatment in PWID can never be overemphasised. The plan is to start engaging different stakeholders and conducting needs assessments to design the focus of effort.
In the past decade, sexually transmitted HCV infections among men who have sex with men (MSM), especially those who were HIV-positive, was increasingly reported worldwide and in Hong Kong. As a well-defined population in linkage to healthcare, people living with HIV are suitable for HCV micro-elimination. Empirical studies showed that scale-up of HCV testing and treatment would be followed by a decrease in the incidence of HCV infections in this key population, signifying the effect of “treatment as prevention”.

ELIMINATION OF HCV-RELATED DEATHS

The mortality reduction target is now justified with the excellent diagnostic and therapeutic interventions for HCV infection. Direct-acting antiviral (DAA) treatment regimens for 8-12 weeks are effective for all HCV genotypes, with a cure rate generally exceeding 90%. In Hong Kong, the estimated diagnosis and treatment rates were just 50.9% and 12.4% respectively, while interferon-based regimens were the first-line therapy and DAA reimbursement was restricted to patients with advanced liver diseases only. Clearly, a generalised use of DAA in HCV treatment is needed for achieving a larger reduction in the disease burden. Since 2019, the HA has started to further extend the use of DAA to milder stages of the disease with a view to cover more patients who are clinically eligible for treatment until HCV is eliminated.

Removing fibrosis restrictions makes it possible to treat more people, but even countries with unrestricted access to DAAs have reported a decline in treatment rates after an initial expansion. To eliminate HCV, it will be essential to find people living with HCV, many of whom have been disenfranchised from the healthcare system, and engage them in care that is adapted to their needs.

HONG KONG VIRAL HEPATITIS ACTION PLAN

Noting all these opportunities and challenges in the elimination of HBV and HCV, the SCVH has been working with different stakeholders to develop an Action Plan for Hong Kong. The Action Plan will set out the direction and strategies to work towards the WHO goals, thereby realising the vision “Hong Kong will be a place where new viral hepatitis infections have ceased, and where everyone with chronic viral hepatitis has access to effective and affordable care and treatment.”

References

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MCHK CME Programme Self-assessment Questions

Please read the article entitled “Elimination of Hepatitis B and C in Hong Kong” by Dr Rebecca Kit-yi LAM and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2020 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. The World Health Organization has set targets to eliminate viral hepatitis as public health threats by 2030.
2. In Hong Kong, the seroprevalence of hepatitis B surface antigen (HBsAg) has been increasing in new blood donors and antenatal women in recent decades.
3. The prevalence of chronic HCV infection is >1% in the general population in Hong Kong.
4. Hepatitis B infection acquired in infancy is less likely to become a chronic infection than that acquired in adults.
5. HBV vaccination can induce protective antibody titres in more than 95% of healthy vaccines.
6. International guidelines recommend the use of tenofovir for women with HBV DNA levels exceeding 200,000 IU per millilitre to prevent mother-to-child transmission of hepatitis B.
7. Chronic hepatitis B can be treated with antiviral agents which can reduce the incidence of liver cancer and improve long-term survival.
8. Sexually transmitted HCV infections among men who have sex with men (MSM), especially those who were HIV-positive, have not been reported.
9. Direct-acting antiviral (DAA) treatment regimens for 8-12 weeks are effective for all HCV genotypes, with a cure rate generally exceeding 90%.
10. Injecting drug use is the major source of incidental HCV infection in Hong Kong.

ANSWER SHEET FOR AUGUST 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Elimination of Hepatitis B and C in Hong Kong

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Name (block letters):____________________________ HKMA No.: __________________ CDSHK No.: _______________
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Answers to July 2020 Issue

Management of Advanced Airway and Lung Diseases
Radiology Quiz

Dr Yan-lin LI
FRCR
Department of Radiology, Queen Mary Hospital

Fig. A healthy 50-year-old man undergoes CT scan of the abdomen as part of a health check. A selected coronal image of the scan is shown above.

Questions
1. What organ is shown?
2. What is the risk of malignancy of the lesion indicated by the blue arrow?
3. On non-contrast CT scan, the Hounsfield Unit of the lesion measured -42. What is the diagnosis?
4. The patient received a follow-up scan two years later, and a new nodule is shown in the right gland. The patient was subsequently diagnosed with primary hyperaldosteronism (Conn’s syndrome) by an endocrinologist. Which lesion is the culprit, left or right?

(See P.40 for answers)
Use of Tenofovir in Further Prevention of Mother-to-child-transmission of Hepatitis B Virus

Dr Wing-cheong LEUNG

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INTRODUCTION

I was trained in Obstetrics & Gynaecology in Hong Kong in the 1990s. Over the many years of my practice, I have always presumed that the universal HBV immunisation programme for newborns in Hong Kong since 1988 after Prof Vivian Wong’s landmark research in the 1980s is already good enough to prevent the mother-to-child-transmission (MTCT) of hepatitis B virus (HBV).

All expectant mothers having antenatal care in the public (Hospital Authority, HA) & private sectors will undergo a routine antenatal blood test to identify their HBsAg (Hepatitis B surface antigen) status. The universal HBV immunisation programme consists of Hepatitis B immunoglobulins (HBIg) to be administered to babies born to HBsAg-positive mothers together with the first dose of HBV vaccine upon delivery (either in labour wards within hours or in postnatal wards within 24 hours after birth). The second and third doses of HBV vaccines will be given mainly in the Maternal & Child Health Centres (MCHC) at 1 and 6 months, respectively. Notably, there is no post-vaccination serological testing performed on infants after completion of the three doses of HBV vaccines to document their HBV immune status.

The World Health Organization (WHO) has the vision to eliminate viral hepatitis as a public health threat by 2030. WHO has estimated that in 2015, 257 million people (> 3% of the global population) are affected by chronic HBV infection, resulting in 900,000 deaths. Mother-to-child-transmission is the most important route of HBV infection, and the infection will usually remain asymptomatic for decades before the life-threatening complications of liver cirrhosis and hepatocellular carcinoma surface.

It so happened that I had the opportunity of representing our College (HKCOG) to attend the Green Ribbon World Hepatitis Day dinner held on 28 July 2018 in Kuala Lumpur. Coincidentally, several months later in 2018, I was recruited to be one of the members of the multidisciplinary Steering Committee on Prevention and Control of Viral Hepatitis co-chaired by the Director of Health, Dr Constance Chan and the Chief Executive of the HA, Dr Leung Pak-yin followed by Dr Tony Ko.

A Clinical Working Group was formed. One of its major tasks is to review the current practice on the prevention of MTCT of HBV in Hong Kong and to explore if the use of antiviral agents in pregnancy could further reduce the MTCT of HBV.

CURRENT SITUATION OF MTCT OF HBV IN HONG KONG

In 2016, the overall prevalence of HBsAg carriers in Hong Kong was 7.8%. By 2016, local women aged 28 years or below should have been covered by the universal HBV immunisation programme (which had been started in 1988), and their prevalence rate of HBsAg positivity was 1.8% while the rate was 3.0% when new immigrants from Mainland China were included. However, in the same year of 2016, 5.2% of pregnant women were HBsAg-positive (dropping to 5.0% in 2017; 4.5% in 2018; and 4.0% in 2019). Despite a 99.8% HBsAg screening coverage for antenatal women, and despite a 99.5% coverage with HBlg and HBV vaccination for live births born to HBsAg-positive mothers (with 98.8% having completed all three doses of HBV vaccination), the overall MTCT rate was still 1.1% from a local study of 641 HBsAg-positive pregnant women by Cheung et al. This MTCT rate of 1.1% is consistent with the data from a U.S. study on 9,252 infants born to HBsAg-positive mothers. In that study, 95% of infants received HBlg and HBV vaccine within 12 hours of birth, and almost all completed ≥3 doses of HBV vaccine series. Hence local data and U.S. data look pale in comparison to the WHO target of <0.1% prevalence of HBsAg-positivity among 5-year-old children by 2030.

In the absence of HBlg and HBV vaccination, about 20% to 40% of infants born to HBsAg-positive mothers are found to be infected by one year of age, with large variations, depending on maternal risk factors such as Hepatitis B ‘e’ antigen (HBeAg) and HBV viral load. The administration of HBlg to newborns at birth together with a complete course of three doses of HBV vaccination has contributed to 75 to 90% reduction in MTCT rate. This reduction of MTCT of HBV could be further reduced by minimising the risk of Immunoprophylaxis Failure (IF). The mechanisms of IF include (i) germline infection at conception; (ii) maternal blood contamination by invasive prenatal tests; (iii) placental infection during pregnancy; (iv) maternal secretion contact during pregnancy; (v) delayed birth dose vaccination; (vi) horizontal transmission in a newborn before the infant could develop a sufficient hepatitis B surface antibody (anti-HBs) response after vaccination; & (vii) mutations in the ‘a’ determinant region of HBV resulting in an immune escape. A high maternal HBV DNA level during pregnancy is the strongest risk factor leading to IF and the IF rate for high maternal viral load (> 8 log10 copies/mL or 2 x 10^7 IU/mL) at 28-30 weeks of gestation is 5.8%. (Remark: 1 IU = 5.82 copies)
THE USE OF ANTIVIRALS IN PREGNANCY TO FURTHER REDUCE THE MTCT OF HBV

Tenoforv is one of the antivirals indicated for the treatment of chronic HBV infection. Resistance to Tenoforv is rare among other antivirals. Tenoforv is a category B drug in the U.S. Food and Drug Administration (FDA) pregnancy categories, which is regarded as safe to be used in pregnancy. Breastfeeding is not contraindicated (although low quality, weaker recommendation). Cessation of antiviral therapy is usually associated with a rebound of viral load, which may be associated with a rise in liver enzymes (such as alanine aminotransferase, ALT). However, a clinically significant flare-up of hepatitis B is uncommon after stopping antiviral therapy and is considered safe in patients with no underlying liver cirrhosis or poor liver reserve. Nevertheless, adequate monitoring after cessation of antiviral therapy is necessary to ensure early identification of cases of hepatitis flare-ups as recommended by international guidelines.

The use of antivirals in HBsAg-positive pregnant women with high HBV DNA levels is recommended by (i) American Association for the Study of Liver Diseases (AASLD); (ii) European Association for the Study of the Liver (EASL); (iii) Asian Pacific Association for the Study of the Liver (APASL); and (iv) Practices Recommendations of the Advisory Committee on Immunization. How about the WHO? The WHO supports countries to evaluate the use of antivirals during pregnancy to further reduce MTCT of HBV, although it has not made any recommendations so far.

LITERATURE REVIEW

In the literature, there are one multicentre, open-labelled, non-randomised study conducted in Taiwan, one meta-analysis and two major multicentre randomised controlled trials (RCTs) conducted in Mainland and Thailand respectively to study the use of Tenoforv during pregnancy to prevent MTCT of HBV: they were published in top-tier medical journals in 2015, 2016 and 2018.

The Taiwan Study (2015)

A total of 118 HBV infected pregnant women with HBeAg positivity, and HBV DNA load > 8 log10 copies/mL (or 2 x 10^7 IU/mL) were enrolled to receive either usual care without antiviral therapy vs Tenoforv 300mg daily from 30 to 32 weeks of gestation until postpartum week 4. HBsAg-positive pregnant women were enrolled based on their willingness to join the control or study arm. All infants received HBIG within 24 hours of delivery and HBV vaccination at 0, 1 and 6 months. The primary outcome was infant HBsAg positivity at 6 months after delivery. The secondary outcome is infant HBsAg positivity at 12 months after delivery. One additional infant in the Tenoforv group became HBsAg-positive at 12 months while the HBsAg status of the other children remained unchanged. This newly infected child was born at term by Caesarean section (twin pregnancy), and the mother had amniocentesis during the pregnancy. The HBsAg-positive rate at 12 months in the Tenoforv and control groups was thus 2/65 (3.08%) vs 6/56 (10.71%); p=0.142. The study was therefore supportive of the use of short-term antiviral therapy in selected HBsAg-positive pregnant women to reduce MTCT of HBV.

The Meta-analysis (2016)

This meta-analysis of 26 studies that enrolled 3,622 HBsAg-positive pregnant women found that the use of antiviral therapy (in addition to HBIG and HBV vaccination) reduced MTCT as defined by infant HBsAg seropositivity (RR=0.3, 95% CI 0.2-0.4) or infant HBV DNA seropositivity (RR=0.3, 95% CI 0.2-0.5) at 6-12 months. There was no increased risk of adverse outcomes among mothers who received antiviral therapy and their newborns. However, this study is limited by concerns regarding the quality of data (as few RCTs were available), potential bias from included cohort studies, and the overall small number of events.

Two major RCTs: The Mainland Study (2016) & the Thailand Study (2018)

These two major RCTs, both published in NEJM, apparently showed conflicting conclusions (Table 1). The devils or indeed the angels might lie in the details!

The negative result of the Thailand Study might have limited generalisability because of the very short median time for the administration of HBIG (1.3 hour) and 1st dose of HBV vaccine (1.2 hour) from birth and the examination of HBsAg status of infants was 6 months instead of the recommended 9 to 12 months. Furthermore, the median HBV DNA level in both groups was 8 log10 copies/mL, that means half of the infants might be at low risk for HBV transmission even if their mothers had not received Tenoforv. The exclusion of mothers with ALT > 30 IU/L might also contribute to the unexpectedly low rate of vertical transmission in the control group. This highlights the need for further research to delineate other potential factors that might influence the MTCT of HBV such as the timing of HBIG administration, the timing & dosage regimen of HBV vaccination, and other factors, e.g. invasive prenatal tests such as chorionic villus biopsy & amniocentesis.

Nevertheless, the MTCT of HBV were both ZERO in the Mainland Study (0/92, per-protocol) and the Thailand Study (0/147). The safety of Tenoforv in pregnancy was ascertain. And the rebound increase of ALT after stopping Tenoforv was mild in the majority of cases.
Table 1. The Mainland vs. The Thailand Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. of subjects</th>
<th>Criteria for recruitment</th>
<th>Randomised 1:1 at 30-32 weeks gestation</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Mainland Study (Pan et al., NEJM 2016)</td>
<td>200</td>
<td>HBeAg +ve and HBV DNA level &gt; 6 log10 copies/mL or 2 x 10^7 IU/mL</td>
<td>Tenofovir 300 mg daily vs. no treatment</td>
<td>HBV DNA level &lt; 6 log10 copies/mL at delivery: (mother)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tenofovir group = 68% (66/97) Control group = 2% (2/100) P&lt;0.001</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>MTCT at 28 weeks postpartum, i.e. HBsAg +ve infants: Tenofovir group = 5% (5/97) Control group = 18% (18/100) P=0.007 [Intention to treat]</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Tenofovir group = 0% (0/147) Placebo group = 2% (3/147) P=0.12</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Birth defects: Tenofovir group = 2% (2/95) Control group = 1% (1/88) P=1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ ALT after stopping Tenofovir: Tenofovir group = 45% (44/97)* Control group = 30% (30/100) P=0.03 *majority of cases were mild</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>↑ ALT (&gt;300 IU/L) after stopping Tenofovir: Tenofovir group = 6% (9/154) Placebo group = 3% (5/157) P=0.29</td>
</tr>
<tr>
<td>The Thailand Study (Jourdain et al., NEJM 2018)</td>
<td>331</td>
<td>HBeAg +ve and ALT &lt; 30 IU/L (median HBV DNA level = 8 log10 copies/mL or 2 x 10^7 IU/mL)</td>
<td>Tenofovir 300 mg daily vs. Placebo</td>
<td>MTCT at 6 months postpartum, i.e. HBsAg +ve infants: Tenofovir group = 0% (0/147) Placebo group = 2% (3/147) P=0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birth defects: Tenofovir group = 2% (2/95) Control group = 1% (1/88) P=1.00</td>
</tr>
</tbody>
</table>

Conclusions

- Supports the use of Tenofovir to prevent MTCT of Hepatitis B
- Does NOT support the use of Tenofovir to prevent MTCT of Hepatitis B

The WAY FORWARD IN HONG KONG

According to a local multicentre study by Cheung et al.\(^5\) on IF of infants born to HBsAg-positive mothers, there were 22.3% and 18.9% of pregnant subjects with HBV DNA level > 7 log10 copies/mL and > 8 log10 copies/mL at 28-30 weeks of gestation respectively. The results showed that the risk of IF with HBV DNA level > 7 log10 copies/mL and > 8 log10 copies/mL was 4.9% and 5.8% respectively and it was reflected from the study that no IF occurred when the maternal HBV DNA level was < 8 log10 copies/mL.

Some calculations have been made according to the prevalence rate and the study results\(^5\) to obtain a clear picture of the current situation in Hong Kong (Table 2).

Table 2. Calculations based on the prevalence rate and local study results. Assume there are 10,000 pregnant women, 520 of them are HBsAg +ve (using prevalence rate = 5.2% in 2016).

A threshold of 2 x 10^7 IU/mL (200,000 IU/mL) is chosen as high HBV DNA which is also the recommendations by AASLD (2018), EASL (2017) & APASL (2015). Using this threshold of HBV DNA level to start Tenofovir for further prevention of MTCT of HBV, assuming a total of 60,000 pregnant women per year in Hong Kong, Tenofovir will be offered to 816 pregnant women (HBsAg +ve with HBV DNA level > 200,000 IU/mL) every year through the eight HA Hospitals with Obstetrics & Hepatology Clinics.

THE ACTION PLAN

After all the preparatory work, the Steering Committee on Prevention and Control of Viral Hepatitis has decided to adopt a universal programme to use Tenofovir to further prevent MTCT of HBV.

The programme has started as a pilot to test feasibility in 2 (QMH & PWH) of the 8 HA Hospitals with Obstetrics & Hepatology Clinics from 1\(^{st}\) quarter of 2020. All HBsAg +ve pregnant women will be tested for HBV DNA, HBeAg, anti-HBe, and L/RFT. Women with high HBV viral load (>200,000 IU/mL) will be given an early referral to the corresponding Hepatology Clinic to discuss starting Tenofovir by 28 weeks gestation to further reduce the risk of MTCT of HBV (irrespective of the HBeAg and LFT status). Women with low HBV viral load (<200,000 IU/mL) will also be given an appointment (triaged by HBeAg and LFT status), usually after their delivery for long term surveillance & treatment of the HBV complications.

The universal programme will be extended to all the 8 HA Hospitals with Obstetrics & Hepatology Clinics. One important aspect of this universal programme to be highlighted is that post-vaccination serological testing (HBsAg & anti-HBs) will be performed to infants after completing the full course of vaccination. This post-vaccination serological testing would be most important

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Abbreviations: GBM—glioblastoma multiforme; TMZ—temozolomide


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to assess the outcome of this new universal programme using Tenofovir during pregnancy on top of HBIG & HBV vaccination to infants from HBsAg +ve pregnant women with high viral load (> 200,000 IU/mL) to further prevent MTCT of HBV in order to achieve the WHO goal to eliminate Viral Hepatitis as a public health threat by 2030.

References


Certificate Course on
Renal Medicine 2020
(Video Lectures)

<table>
<thead>
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<th>Date</th>
<th>Topics</th>
<th>Speakers</th>
</tr>
</thead>
</table>
| 3 Sep    | Kidney Involvement in Multi-System Disorders | Dr Desmond Yat-hin YAP | Clinical Associate Professor  
University of Hong Kong |
|          | ABC of Hemodialysis Therapy                 | Dr Genev Mei-wa TONG | Consultant in Nephrology  
Hong Kong Baptist Hospital |
| 10 Sep   | Update and Management of Acute Kidney Injury | Dr Chun-hay TAM | Associate Consultant  
Department of Medicine & Transplantation  
Queen Elizabeth Hospital |
|          | Nutritional Management in Kidney Diseases   | Ms Cherry Pui-yee LAW | Dietitian  
Park Lane Yuen Nethersole Eastern Hospital |
| 17 Sep   | Common Investigation Tests for Renal Disease Including Approach to Proteinuria and Haematuria | Dr Sze-kit YUEN | Associate Consultant  
Department of Medicine & Transplantation  
Canina Medical Centre |
|          | Update and Management of Glomerular Disease | Dr Elaine Tsz-ing HO | Associate Consultant  
Department of Medicine  
St. Olav's Hospital |
| 24 Sep   | Update on Diabetic Nephropathy               | Dr Maggie Kam-man MA | Associate Consultant  
Department of Medicine  
Queen Elizabeth Hospital |
|          | ABC of Peritoneal Dialysis Therapy          | Dr Joseph Ho-sing WONG | Associate Consultant  
Department of Medicine  
Queen Elizabeth Hospital |
| 8 Oct    | Update and Management of Chronic Kidney Disease | Dr Wing-fai PAN | Associate Consultant  
Department of Medicine & Transplantation  
Prince of Wales Hospital |
|          | ABC of Renal Transplantation                | Dr Ka-fai YIM | Associate Consultant  
Department of Medicine & Transplantation  
Prince of Wales Hospital |
| 15 Oct   | Update and Management of Hypertension       | Dr Wai-yan LAU | Associate Consultant  
Department of Medicine & Transplantation  
Queen Elizabeth Hospital |
|          | Drug Prescribing in Renal Failure           | Dr Anthony Kai-ching HAU | Associate Consultant  
Department of Medicine & Transplantation  
Princess Margaret Hospital |

Date : 3, 10, 17, 24 September & 8, 15 October, 2020 (Thursday, skip 1 October)  
Time : 7:00 pm – 8:30 pm  
Course Feature : Video lectures (with Q&A platform)  
Course Fee : HK$1,000 (6 sessions)  
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong  
Tel.: 2527 8898  
Fax: 2865 0345  
Email: vienna.lam@fmshk.org  
Application from can be downloaded from website : http://www.fmshk.org
High Resolution Anoscopy for the Management of HPV-Associated Anal Intraepithelial Neoplasia

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INTRODUCTION

Human Papillomavirus and Anal Cancer

Human papillomavirus (HPV) infections are the most common sexually transmitted infections worldwide. HPV is a non-enveloped double-stranded DNA virus that infects mucosal and cutaneous keratinocytes. There are more than 180 subtypes of HPV, of which 40 types infect the anogenital region. These subtypes can usually be categorised into high- vs low-risk in terms of their oncologic potential. Most sexually active males or females will acquire HPV soon after sexual debut. 90% of the infection is silent and will resolve spontaneously. There are several factors associated with persistent infection, and they are shown in TABLE 1. The longer the duration of an HPV infection, the greater the chance that it will lead to cellular changes.

The importance of persistent HPV infection lies in its association with cancer causation. Evidence for cervical cancer has been firmly established. Anal intraepithelial neoplasia (AIN) is a potential precursor lesion of anal squamous cell carcinoma. Similar to cervical intraepithelial neoplasia (CIN), AIN is causally linked to persistent infections with high-risk HPV types such as HPV16 or HPV18. There is ample evidence for HPV infection as precursor infection for anal intraepithelial neoplasia (AIN) and anal cancer. HPV prevalence among patients with AIN is over 90%. A large meta-analysis found that among patients with cervical, vulvar and anal cancer, those with anal cancer had the highest prevalence of HPV infection (84.3%). Furthermore, the amount of HPV DNA is higher in those with high-grade AIN than low-grade AIN, suggesting its biologically plausible role in causing the malignancy.

Table 1. Factors associated with persistent HPV infection (Adapted from Rev Obstet Gynecol 2008)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th><em>behaviours</em></th>
<th>Medications</th>
<th>Co-infection</th>
<th>HPV infection characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviours</td>
<td>Multiple sexual partners</td>
<td>Immunosuppression</td>
<td>Human immunodeficiency virus (HIV)</td>
<td>High risk HPV type 16, 18</td>
</tr>
<tr>
<td></td>
<td>Men who have sex with men</td>
<td>No HPV vaccination</td>
<td>Multiple HPV subtype infections</td>
<td>High viral load</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>Oral contraceptive use</td>
<td>Other sexually transmitted infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited medical care</td>
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</table>

WHO ARE THE AT RISK GROUP?

Anal cancer is uncommon, with an incidence rate of around 2 per 100,000 of the general population, but incidence rates have been steadily increasing over the last three decades. It is more common in females than in males.

Anal cancer is increasing significantly among some groups of people, especially those infected with HIV, men who have sex with men (MSM), women with a history of cervical, vaginal or vulvar cancer, tobacco smokers, and people who are immunocompromised due to organ transplants, steroid use, or the use of any medications that suppress the immune system. In human immunodeficiency virus (HIV)-infected MSM, anal HPV prevalence is more than 90%, and infections with multiple HPV types are common. Consequently, HPV-associated anogenital malignancies occur with high frequency in patients with HIV infection. Although anal cancer is not an AIDS-defining cancer, it is 30-100 times more common in HIV-positive individuals. Studies have indicated that a low CD4 count in HIV-positive individuals is a risk factor for AIN and invasive anal cancer.

WHAT IS ANAL INTRAEPITHELIAL NEOPLASIA AND HOW TO RECOGNISE IT?

Anal squamous dysplasia refers to a spectrum of disease ranging from low-grade intraepithelial lesions (LSIL) to high-grade squamous intraepithelial lesions (HSIL) to invasive anal squamous cell carcinoma of the anus (SCCA). They can involve both the perianal skin and anal canal. ‘Intraepithelial’ in anal intraepithelial neoplasia (AIN) refers to the abnormal cells not having gone further than the epithelium or the lining of the anus. AIN can either be LSIL or HSIL. Inside the anal canal, the histopathologic manifestations of HPV infection are most commonly detected at the anal transition zone (ATZ), where the rectal columnar epithelium and anal squamous epithelium meet (known as the squamo-columnar junction, SCJ) (Fig. 1). The anus and cervix also share embryological origins and susceptibility to HPV infection, which might also explain the similarities between these malignancies.

LSIL usually goes away on its own, without treatment. But some of them associated with an increased risk of HSIL are less likely to go away on their own, with approximately one in ten chance of becoming a
cancer over approximately five years\textsuperscript{20,21}. But there is heterogeneity, and the rate is highest in high-risk populations. The rate of progression of AIN to invasive anal cancer more closely resembles the natural history of vulval intraepithelial neoplasia, with expected malignant transformation in about 10% of immunocompetent patients over five years\textsuperscript{22}. 

Patients with AIN are often asymptomatic. Symptomatic patients may present with pruritus or anal discharge. Suspicious lesions may be raised, plaques, scaly, fissured, or eczematous. The colour can be white, erythematous or pigmented\textsuperscript{23}.

Patients who describe perianal symptoms consistent with AIN or anal cancer require examination of the perineum, digital rectal examination, and examination of the inguinal area for palpable nodes. When AIN is found, it is important to examine other sites including vulva, vagina and cervix in women and the penis in men, because of the multi-zonal nature of the disease\textsuperscript{24}. The vice-versa should apply to patients detected to have disease involving vulva, vagina and cervix to have a lower threshold of screening for AIN. There is a misconception that anal HPV infection was invariably associated with anal intercourse. In fact, sex does not have to occur for the infection to spread, and most women who have AIN or anal cancer did not have a history of anal intercourse. Skin-to-skin contact with an area of the body infected with HPV is all that is needed for infection to spread. The virus can be spread through genital-to-genital contact or even hand-to-genital contact. HPV infection can also spread from one part of the body to another, for example, from the genitals to anus\textsuperscript{25}. The finding that it is more common in women who clean themselves from front to back after voiding urine is a case in point\textsuperscript{26}.

\section*{WHAT IS High-resolution Anoscopy?}

High-resolution anoscopy, or HRA, is a procedure that allows for examination of the anal canal and surrounding skin using a colposcope. The 10-40 times magnifying power of the colposcope allows for the direct visualisation of the mucosal surface of the anal canal and the surrounding skin of the perianal area. In addition, staining up with acetic acid and Lugol's iodine will enable lesions which are otherwise invisible to the naked eyes to be picked up for biopsy for confirmation of histology.

HRA is well known for its steep learning curve, and hence quality assurance is of vital importance in ensuring proper care. For that, the International Anal Neoplasia Society (IANS) has defined minimum standards for service to guide HRA practitioners on the set-up and implementation of high-resolution anoscopy, the provision of information to patients, staffing, infection control, medical notes, and follow-up referrals to and communication with a team of specialists\textsuperscript{27}.

\section*{WHO SHOULD HAVE HRA?}

- People who have a higher risk of developing anal cancer. They include both men and women who are immunosuppressed; this could be due to HIV infection, organ transplants, long term steroid use or other medicine that suppresses immune function, or any other condition that affects the immune system.
- People who have a history of anal dysplasia (precancerous changes) or cervical or vulval dysplasia (women).

\section*{WHY IS IT DONE?}

When Pap smear was first introduced to screen for precancerous changes in the cervix of women, it was based theoretically on the pathological progression of precancer changes to cancer. It was after decades of screening that revealed the usefulness of Pap smear in the reduction of cervical cancer. Biological and epidemiological evidence has demonstrated that anal cancer and cervical cancer share lots of analogy and persistent high-risk type HPV infection is even a stronger predictor for anal cancer. Clinical approach to the diagnosis of AIN also borrows from the cervical cancer model and includes the application of colposcopy to the evaluation of anal and perianal region\textsuperscript{28}. The success of cervical cancer screening has led to the use of colposcopy as a template for anal cancer screening in high-risk groups.

A retrospective study demonstrated that anal carcinoma developed at previously biopsied sites of high-grade dysplasia in 27 out of 72 anal cancers studied (37.5\%), illustrating the potential for the development of anal squamous cell carcinoma from high-grade anal dysplasia\textsuperscript{29}. In this study, nearly half of the HIV-infected MSM with HSIL who developed anal cancer were asymptomatic\textsuperscript{29}. Evidence to support the use of HRA for detection and treatment in the surveillance of AIN exists and strongly suggests that it is beneficial, resulting in reduced rates of cancer progression\textsuperscript{30}. Pilot data demonstrated a 5.72-fold reduction in local disease failure rates of patients with T1-T3 tumours; these data, therefore, suggested that use of HRA for detection and treatment in surveillance of anal cancer patients will help prevent local, regional relapse at the anal site\textsuperscript{30}. Hence the objective of HRA is to detect precancer lesion early. HRA will also allow treatment to be performed to prevent the HSIL from turning into cancer.
Anal cytology is only 47 to 70% sensitive in picking up precancerous lesions in HIV-negative MSM. In high-risk population such as HIV-positive MSM, anal cytology can be inaccurate and has been shown not to correlate with histology. Testing of high-risk human papillomavirus strains 16/18 improves specificity and positive predictive value over cytology for AIN screening. Patients testing positive for strains 16/18 are at high-risk for HSIL and should undergo high-resolution anoscopy regardless of the cytology result.

HRA has been recommended by some as a tool for screening in high-risk patients. Apart from a better sensitivity and specificity for picking up abnormal lesions, HRA also allows ablative therapy to be done. However, HRA involves higher demand in terms of expertise and cost.

A large retrospective review from 2015 showed that patients followed with standard anoscopy or HRA every 3-12 months had lower rates of progression of AIN to anal cancer, compared to epidemiologic data. Standards and protocols for anal cancer screening are not widely promulgated. The AIDS Institute of the New York State Department of Health has established formal screening guidelines for HIV-positive individuals. It recommends routine annual examination of the anus in all HIV-infected adults and cytologic (pap) testing in higher risk HIV-positive patients such as men who have sex with men (MSM), those with a history of genital infection, and women with cervical or vulvar dysplasia. A colonoscopy does not screen for anal cancer and is not an acceptable alternative to HRA.

The U.S. Department of Health and Human Services (HHS) AIDS Info website in 2018 recommended that positive cytology requires follow-up with HRA and that visible lesions should be biopsied. Patients should be referred to expert centres where diagnostic and treatment procedures using HRA can be performed. The high recurrence rates of AIN also warrant ongoing post-treatment surveillance.

For transplant patients, there is a recommendation for annual anal cytology targeting at those with a history of anal intercourse and a history of cervical dysplasia. Abnormal cytology needs a referral to HRA for biopsy and treatment.

**HOW IS IT DONE?**

There is no special preparation needed for the assessment. The procedure is performed on an outpatient basis. Starting 24 hours before the examination, avoid using any douches, enemas or creams that are applied to the anal canal. It is also important to avoid anal sex.

The patient will be asked to remove the lower half of his/her clothes and given a gown opening at the back. There are several positions for performing HRA. In the UK, it is done in a lithotomy position (Fig. 2). In the Netherlands, it is performed in lithotomy position too, but the legs are elevated much higher than those in UK (Fig. 3). In USA, it is either performed in knee-chest position (Fig. 4) or lateral position. In Australia, it is performed in a lateral position (Fig. 5). Some patients may prefer lateral position as they claim to be less vulnerable in that position. The choice of the position depends on the habits and practice of the operators as well. Personally, I find the lithotomy (especially with the end of the pelvic table tilted up considerably) or knee-chest position can expose the SCJ better as the mucosal folds tend to gravitate towards the colon end and provide a better view. Knee chest position can be challenging for some patients who have knee problems. Hence, I adopt the lithotomy position in Hong Kong (Fig. 6).
Before the proper HRA, an anal Pap smear is performed if not done before. Taking an anal pap smear involves gently pushing a fine thin brush into the anal canal to obtain cells from the lining of the anus and collect in liquid medium for cytology. Then, the clinician will examine the anal canal with a finger to feel inside the anus and rectum for abnormal growths and will also examine the skin around the anus for any abnormalities (digital anorectal examination; DARE). As part of DARE, it is important to document any palpable mass lesion, indicating the distance from the anal verge and the proportion of the anal circumference that it occupies. Inspect the glove for blood from the anal canal.

For the HRA, a proctoscope will be coated with a lubricant and inserted about two inches into the anus. A cotton swab covered with mild (5%) acetic acid will be inserted through the proctoscope into the anus. Acetic acid is generously and continually applied during the examination to highlight areas of disease. The acetic acid on the cotton swab will cause any abnormal cells to turn white; these are called 'Acetowhite' areas. Acetowhite areas/lesions with specific vascular characteristics like punctuation or honeycomb patterns are highly suggestive of high-grade disease. (Fig. 7) Lugol’s iodine is then used to highlight Lugol non-uptake areas. With the use of a magnifying colposcope, the clinician performing the examination can detect abnormal areas using the characteristics described above. Should the patients want, they can observe the anoscopy image on the computer screen while the procedure is being performed. After a careful and thorough examination, the doctor will decide whether to take one or more biops(ies) from the anal canal and the perianal area. A local anaesthetic will be injected before the biopsy is taken to help minimise any discomfort.

The total time of the procedure is between 20-40 minutes. The procedure is usually very well tolerated with mild, if any, discomfort. Significant risks, such as bleeding or infection, are extremely rare. HRA can also be used to direct therapy. Ablative therapy using infrared coagulation, hyfrecation or laser can be performed during HRA.

**WHEN IS IT DONE?**

Screening has been found to be cost-effective for AIN\(^42\). Various infectious disease societies have made recommendations for annual cytology for HIV-positive patients, especially those who are MSM, or have a history of cervical cancer\(^43\). For timing of subsequent surveillance, there is no established consensus, but most societies recommend yearly surveillance for HIV-positive males, and every 3-6 months for those with low- or high-grade AIN\(^44\). Fig. 8 showed the recommended algorithm for the diagnosis and management of AIN by Department of Health of New York State, USA\(^35\).

When high-grade lesions are found, they can be treated either by topical agents or by ablative therapies. The primary topical agents are imiquimod, TCA, and 5-FU. Imiquimod is a synthetic immune modulator that works by upregulating the patient's immune system to combat the virus. It has been shown to downgrade high-risk lesions to low-risk lesions among HIV-positive patients\(^45\). In a randomised study, 61% of patients had an absence of high-risk lesions sustained at 36 months with imiquimod treatment\(^46\). The major side effects include treatment area reactions such as irritation and burning pain. TCA has a good safety profile with few major side effects. It can be applied during the examination, and is well-tolerated. Two retrospective
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studies of small populations of biopsy-confirmed high-grade AIN lesions reported rates of HSIL regressing to LSIL or complete resolution in 71%-79% of cases\(^47,48\). 5-FU is a chemotherapy agent that inhibits DNA synthesis and, when applied topically, can clear AIN. Prospective data showed complete clearance of 90%, with a recurrence rate of 50% at 6 months\(^49\). Side effects include hypopigmentation or skin irritation.

Ablative therapies, including infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfrecator are well tolerated. Repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN2-3. Infrared coagulation (IRC) was proven to have moderate efficacy in the treatment of HSIL in patients who are HIV-seropositive in a retrospective study\(^50\). It was safe and well-tolerated in the HIV-positive population in a prospective study\(^51\).

Hyfrecation (electrocautery ablation) is also commonly used to treat anal HSIL. It has a similar efficacy profile to IRC\(^52\). Some clinicians prefer it over IRC because it may be faster than IRC, particularly for large and keratotic lesions. It is also easier to use than IRC for the perianal disease.

The efficacy of hyfrecation was addressed in a retrospective study in HIV-positive patients where at one-year post-ablation, about 45% of patients developed local recurrence. No patient developed invasive squamous cell carcinoma of the anus (SCCA)\(^53\).

Taken together, topical therapy appears to be generally well-tolerated and offers reasonable efficacy, although a substantial portion of patients will not respond and others will recur. In many centres, topical therapy is utilised as an adjunct to local ablative therapy. At one centre, 248 patients were followed with exams and serial ablative procedures under HRA and supplemental topical treatments. 80% clearance of HSIL was demonstrated and only 1.2% of the patients developed anal cancer\(^54\).

Currently, a prospective randomised study called Anal Cancer HSIL Outcomes Research (ANCHOR) to determine whether screening and treatment of HSIL are effective in reducing subsequent anal cancer in HIV-positive men and women compared with active monitoring via regular exams (including anal cytology combined with HRA and biopsy of any concerning lesions) vs observation is underway in 12 sites in the United States. Treatments can include imiquimod, fluorouracil, electrocautery, and laser therapy. The study will be able to answer questions like the best strategy for AIN surveillance and the efficacy and safety of different treatment modalities\(^55\).

**ROLE OF HPV VACCINATION**

HPV vaccine is currently recommended only as a preventive immunisation for youth between the ages of 9 to 26. US CDC recommends it for people of all gender identities and sexual orientations, starting at age 11 or 12. Since it is intended to be given before sexual activity begins, it can be given as early as nine years of age. ACIP also recommends vaccination through age 26 years for those who were not adequately vaccinated previously, including gay, bisexual, and other men who have sex with men, transgender people, and immunocompromised persons (including those with HIV infection)\(^56\).

A trial using quadrivalent vaccines among MSM showed that the incidence of anal SIL associated with HPV 6, 11, 16, or 18 was decreased by 78% and the incidence of persistent HPV infection of relevant types was decreased by 95% in those receiving the vaccine compared with those receiving placebo (per protocol efficacy). 165 (27.4%) men were seropositive or HPV DNA–positive for HPV-6 or 11, 99 (16.4%) for HPV16, and 68 (11.3%) for HPV-18. Hence HPV vaccine is useful for prevention of AIN and should preferably be given before sexual activity begins\(^57\).

Administration of the vaccine after the diagnosis of AIN in order to assist with prevention in the future has been
studied. Retrospective data showed that vaccination could lower the rates of HSIL in MSM with recurrent AIN\(^\text{TM}\). A randomised trial involving MSM found the rates of AIN were lower in the vaccine group, while they also had a significantly lower risk for persistent HPV infection following vaccination\(^\text{TM}\). Therefore, patients with AIN may benefit from the vaccine though it is considered an off-label use of the vaccine.

Primary prevention by administering the 9-valent HPV vaccine to girls and boys prior to the onset of sexual activity is most effective for prevention of almost all squamous cell carcinoma of the anus (SCCA). In addition, the 9v HPV vaccine may be helpful in preventing recurrent HSIL and possibly the progression to SCCA, especially in individuals at increased risk for SCCA including all HIV-positive men and women, HIV-negative MSM, and women with a history of CIN3 or cervical cancer.

**FINAL REMARKS**

HRA of the anal region, analogous to colposcopy of the cervix, is a technique that is not well-known in the medical and surgical fraternity. There is much potential room for improvement in general knowledge about the prevention, diagnosis and treatment of chronic HPV infection, AIN and anal cancer among medical practitioners and patients in high-risk groups alike. Specialists taking care of high-risk patients need to be aware of this disease entity and educate patients about the disease and prevention methods. This applies especially to gynaecologists and oncologists taking care of patients with other HPV-associated cancers; nephrologists or transplant physicians taking care of transplant patients and rheumatologists and other physicians taking care of patients on immunosuppressants.

To facilitate communication and better understand risks, healthcare providers need to learn how to comfortably take a proper sexual history in a non-judgemental way, regardless of stated or assumed sexual orientation, to better understand who is at risk. In patients with AIN or SCCA, Smoking cessation should be encouraged. Women should be made aware that anal HPV recovery does not mean anal intercourse and should be encouraged to abash shame associated with the condition and come forwards to seek medical help if they notice any anal symptoms. There is a high correlation between cervical and anal cancer risk in women. For MSM, due to the high rate of sexually transmitted diseases and anal cancer among this population, a comprehensive STDs screening and prevention strategy inclusive for HPV should be in place.

References

12. Chin-Hong PV & Reid GE on behalf of AST Infectious Diseases Community of Practice. Human Papilloma Virus Infection in solid organ transplant recipients. Guidelines from the American Society for Transplantation Infectious Diseases Community of Practice. Clinical Transplantation 2019;00: e13590.

The Hong Kong Medical Journal Vol 25 No 8 August 2020
Dovato is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with non-antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato.
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**Indicated for:**
- Complicated Urinary tract infections
- Complicated acquired Pneumonia
- Complicated intra-abdominal infections
- Complicated skin and skin structure infections
- Acute pelvic infections
- Prophylaxis of Surgical site infection following elective colorectal surgery

**Covering a wide range of bacteria included:**
- **Gram-positive**
  - Staphylococcus aureus
  - Streptococcus agalactiae
  - Streptococcus pneumoniae
  - Streptococcus pyogenes
  (Note: Methicillin-resistant Staphylococcus are resistant to INVANZ. Many strains of Enterococcus faecalis and most strains of Enterococcus faecium are resistant.)
- **Gram-negative**
  - Escherichia coli
  - Klebsiella pneumoniae
  - Haemophilius influenzae
  - Moraxella catarrhalis
  - Proteus mirabilis
- **Anaerobes**
  - Bacteroides fragilis
  - Eubacterium spp
  - Prevotella spp
- **Clostridium spp** (excluding C.difficile)
- **Peptostreptococcus spp
- Porphyromonas asaccharolytica**

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*ESBL = Extended Spectrum β-lactamase  
*For adult aged 13 and older

**Reference:** 1. Hong Kong INVANZ Product Circular

**INVANZ** Selected Safety Information

**Indications:**
- INVANZ is indicated for the treatment of patients with moderate to severe infections caused by susceptible microorganisms, as well as initial empiric therapy prior to the identification of causative organisms in the infections listed below:
  - Complicated Intra-Abdominal Infections
  - Complicated Skin and Skin Structure Infections, including diabetic foot infections without osteomyelitis
  - Community Acquired Pneumonia
  - Complicated Urinary Tract Infections including pyelonephritis
  - Acute Pelvic Infections including postpartum endometritis, septic abortion and post-surgical gynecologic infections
  - INVANZ is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

**Contraindications:**
- INVANZ is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class in patients who have demonstrated anaphylactic reactions to beta-lactams.
- Due to the use of ticarcillin HCl as a diluent, INVANZ administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block (Ticarcillin HCl is the diluent for intramuscular administration of INVANZ).

**Precautions:**
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam. Before initiating therapy with INVANZ, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to INVANZ occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment.
- Seizures and other CNS adverse events have been reported. Seizures, irrespective of drug relationship, occurred in 0.5% of patients during therapy plus 14 day follow-up period. Most common in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Close adherence to dosage regimen is urgent in patients with factors predispose to convulsive activity. Anticonvulsant therapy should be continued. If local tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and the dosage of INVANZ re-examined to determine whether it should be decreased or discontinued.
- The concomitant use of ticarcillin and vancomycin/vancomycin/sodium is generally not recommended. Anti-bacterial other than ticarcillin should be considered to treat infections in patients whose severs are well controlled on vancomycin or vancomycin sodium.
- As with other antibiotics, prolonged use of INVANZ may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient’s condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.
- Pseudomembranous colitis has been reported with nearly all antibiotics including, erythromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
- Caution should be taken when administering INVANZ intramuscularly, to avoid inadvertent injection into a blood vessel.

**Adverse Events:**
- Most adverse experiences reported in clinical studies were described as mild to moderate in severity. The most common drug-related adverse experiences reported during parenteral therapy in patients treated with erythromycin were diarrhea, nausea and vomiting. Other common side effects include: phlebitis/thrombophlebitis, vomiting, infusion site erythema, infusion site pain, infusion site swelling, rash, etc.
- For detailed adverse events, please consult the prescribing information.

Before prescribing INVANZ, please read the Full Prescribing Information.

**MSD**

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Updates on COVID-19 and Therapeutics—How far does the Evidence Go?

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BACKGROUND

In December 2019, a novel coronavirus emerged in Wuhan, China, and rapidly spread throughout other cities in the Mainland. Subsequently, the virus was identified as SARS-CoV-2 by scientists in China, as the cause of a respiratory illness designated coronavirus disease, or COVID-19. Retrospective analysis revealed that the earliest confirmed cases had an epidemiological link to a wholesale food market in Wuhan, while some did not. By May 29, 2020, more than 5.8 million COVID-19 cases were diagnosed worldwide. The number of patients is highest in the USA, with more than 1.7 million cases, followed by Brazil and Russia. Death tolls related to COVID-19 exceeded 360,000 globally. In Hong Kong, the first patient, with a history of travel to Wuhan, was diagnosed on January 22, 2020, with fever and upper respiratory symptoms at presentation. By May 27, 2020 there was an accumulated number of 1,067 confirmed cases with four deaths. The majority of patients had recovered and were discharged from the hospital.

Clinical trials of COVID-19 are ongoing and searching for a definitive therapeutic agent. Some treatments being tested are based on previously demonstrated efficacy on the severe acute respiratory disease (SARS) and Middle East respiratory syndrome (MERS).

CLINICAL FEATURES AND RISK FACTORS

Transmission of COVID-19 occurs by close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces. Under certain circumstances, it may be transmitted via aerosol. The incubation period is mostly 5-6 days but can be up to 14 days. Less than 50% of confirmed patients presented with fever on admission. In a large cohort of 1,099 patients with laboratory-confirmed COVID-19 from 552 hospitals in mainland China, fever was only present in 43.8% on admission and 88.7% during hospitalisation. Cough, sputum, and fatigue were common symptoms while diarrhoea was infrequent. Lymphopenia was present in 83.2% of patients. Common comorbidities in severe cases included hypertension and diabetes. For treatment outcome, 6.1% of patients required mechanical ventilation, and the overall mortality rate was 1.4% from this cohort. In another cohort involving 5,700 patients in New York City, only 30.7% of patients had a fever at triage. During hospitalisation, 14.2% required ICU care, 12.2% received mechanical ventilation. The overall mortality was 21%. Loss of smell (anosmia) or loss of taste (ageusia), if present, is often noticed preceding the onset of respiratory symptoms. For high-risk patients’ identification, a meta-analysis revealed that patients with chronic obstructive pulmonary disease (COPD) had an increased risk of severe complications and higher mortality with COVID-19 infection. Other risk factors for mortality include advancing age, obesity and comorbidities such as chronic liver disease or chronic kidney disease.

CLINICAL MANAGEMENT

General Management

Patients with suspected or confirmed COVID-19 infection in Hong Kong were kept in Airborne Isolation Rooms (AIR) in hospitals. For mild disease, symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration was given. Empirical antibiotics should not be prescribed unless there is clinical suspicion of concomitant bacterial infection. Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock and respond immediately with supportive care interventions.

ANTIVIRALS, IMMUNOMODULATORS AND OTHER ADJUNCTIVE THERAPIES

Hydroxychloroquine (HCQ) and Chloroquine (CQ)

Chloroquine is a widely used drug for malaria infection and autoimmune diseases. The pharmacological activity of CQ and HCQ was tested using SARS-CoV-2 infected Vero cells. HCQ was found to be more potent than CQ in vitro. In mid-March, France approved the commencement of HCQ in severe cases of COVID-19. This was based on an open-label non-randomised clinical trial using HCQ and/or azithromycin as a treatment for COVID-19. Fourteen of 20 cases (70%) of the HCQ treated group showed a significant viral suppression to undetectable level versus the untreated group (12.5%) at day six post inclusion. Subgroup analysis showed that those given HCQ + Azithromycin...
(n=6) was associated with 100% viral suppression. However, more recent multinational registry analysis, comprising data from 96,032 patients from 671 hospitals in six continents revealed a contradictory finding. The use of hydroxychloroquine or chloroquine, either alone or with a macrolide, was associated with a decreased in-hospital survival and an increased occurrence of ventricular arrhythmia12.

As a result, the World Health Organization (WHO) suspended the HCQ arm within the agency’s Solidarity Trial on May 25, 2020. However, the suspension was lifted after concerns on the methodologic and data integrity of the study13. The three authors of the paper have since issued a statement in the ‘Lancet’ withdrawing the HCQ article because of the difficulty in verifying the primary data sources.

Remdesivir

Remdesivir (GS-5734), an inhibitor of the viral RNA dependent RNA polymerase with inhibitory activity against SARS-CoV and MERS-CoV, was identified as a potential candidate therapeutic for COVID-19 with in vitro activity against SARS-CoV-214. A double-blind, randomised, placebo-controlled trial (RCT) done in China involving 237 patients (158 given Remdesivir & 79 given placebo) did not show any significant clinical improvement15. However, this study was criticised because it was underpowered. Subsequently, a bigger RCT conducted by the US National Institute of Allergy and Infectious Diseases (NIAID) enrolled 1,063 patients, who were randomly assigned to receive a 10-day course of intravenous Remdesivir or placebo. This study showed a significantly better clinical outcome with Remdesivir. The median time to recovery for patients treated with Remdesivir (11 days (95% confidence interval [CI], 9 to 12)) was significantly shorter than those in the placebo group (15 days (95% CI, 13 to 19)), in adults hospitalised with COVID-19 and evidence of lower respiratory tract infection16. The study also demonstrated that there was no difference in clinical outcome between a 5-day and a 10-day course of Remdesivir in the treatment of severe cases of COVID-1917. In Hong Kong, about 30-40 patients were given Remdesivir under a clinical trial setting in 3 different centres.

Lopinavir-Ritonavir, Ribavirin and Interferon Beta-1b

Lopinavir-ritonavir, a human immunodeficiency virus (HIV) type 1 protease inhibitor, in combination with ribavirin, was shown to reduce the risk of adverse clinical outcomes among patients with SARS in 200318. An animal study has demonstrated that mammals treated with Interferon (IFN) beta-1b may have a better clinical, radiological and pathological outcome than untreated animals19. A RCT was conducted in Wuhan, China to determine the efficacy of lopinavir-ritonavir on 199 hospitalised patients with SARS-CoV-2. No benefit was observed with treatment beyond standard care. However, the median time from symptom onset to randomisation was 13 days (interquartile range 11-16). This rather late symptom onset to randomisation day, raised the question of whether the insignificant treatment efficacy was related to late prescription in these patients (more than a week of symptom onset)20.

Hung et al. revealed the result of a local, multicentre, prospective, open-label, randomised trial in adults with COVID-19 in Hong Kong. A total of 127 patients were recruited; 86 assigned to the combination therapy group and 41 assigned to the lopinavir-ronitavir monotherapy group as the control. Early use of triple antiviral therapy was safe, and no significant differences in the incidence of adverse events were noted. Triple antiviral therapy was superior to the control group, in terms of alleviating symptoms (4 days vs 8 days) and shortening the duration of viral shedding (7 days vs 12 days) and hospital stay (9 days vs 14.5 days) in patients with mild to moderate COVID-19. These outcomes were even more significant when the triple therapy was started less than or equal to 7 days after onset of symptoms21. This combination therapy strategy is still ongoing in hospitals in Hong Kong. Future clinical studies using a double antiviral therapy with interferon beta-1b as a backbone are warranted.

Tocilizumab

Monoclonal antibodies directed against inflammatory cytokines could be an adjunct therapy for severe cases of COVID-19. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is mainly used to treat rheumatoid arthritis and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Studies have shown that levels of inflammatory mediators are associated with the clinical severity of the COVID-19. It has been used in a small series of severe COVID-19 cases with the aim of alleviating cytokine storm. In one study, 21 patients received a single dose of tocilizumab. All patients became afebrile on the first day after tocilizumab and remained stable thereafter. 75% had lowered their oxygen requirement within five days of treatment. Radiologic improvement occurred in 91% of patients. Lymphocyte counts returned to normal in 52.6% of patients22. Several RCTs of tocilizumab are in progress. In Hong Kong, a few ICU cases of COVID-19 were given tocilizumab.

Corticosteroids

The routine use of systemic corticosteroids in moderate to severe COVID-19 patients is not recommended9. Although corticosteroids can decrease the host inflammatory responses in the lungs, it also results in a delay in viral clearance and an increase in the risk of secondary infections. One systematic review showed no significant difference in survival, hospitalisation duration, ICU admission and use of mechanical ventilation among patients given systemic corticosteroids23.

CONCLUSION

The SARS-CoV-2 pandemic continues to pose a significant threat to global public health. Most patients will recover with supportive therapy alone. However, for patients with moderate or severe diseases, especially for those with risk factors, combination therapy of interferon beta-1b and lopinavir-ritonavir may be considered. For patients with severe disease,
Remdesivir may provide a better clinical outcome. More future RCTs are needed to search for evidence of effective therapy against COVID-19 infection.

References
10. Guangdong, Hebei, and Hubei Provinces and the city of Wuhan report that their cumulative number of COVID-19 cases in February 2020 is 19,000.
Certificate Course on

Mental Health 2020
(Video Lectures)

Objectives:
This course aims to introduce to the allied health professionals and Registered / Enrolled Nurses (General) on the aetiology, course, and management of common psychiatric disorders in Hong Kong. Each topic will be delivered by a specialist psychiatrist who has extensive clinical expertise and academic knowledge in that particular area. After the course, the participants will have better understanding about the course, nature and current evidence-based treatments of various common psychiatric disorders. The course will be suitable for allied health professionals and Registered / Enrolled Nurses (General) working in mental health fields, general hospital settings, as well as social care settings in the community.

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<td>Anxiety and phobias</td>
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<td>25 Sep, 2020</td>
<td>Common psychiatric disorders in children and adolescents</td>
<td>Dr. Tam Fung-ling, Venus Private Psychiatrist</td>
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Date: 21, 28 August & 4, 11, 18, 25 September, 2020 (Every Friday)
Time: 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform)
Language Media: Cantonese (Supplemented with English)
Course Fee: HK$1,000 (6 sessions)
Certificate: Awarded to participants with a minimum attendance of 70%
Enquiry: The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898  Fax: 2865 0345  Email: vienna.lam@fmshk.org

CME / CNE / CPD Accreditation in application
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Sound Therapy: from Polyvagal Theory to Practice

Dr Andrew Tin-yau WONG
Specialist in Infectious Disease

Mr Anthony B.L. NEC
B.Com(Hon), D.ST, D5, ACMC
Principal, International Sound Healing Academy, UK

Stress is everywhere. Most people would yearn for being at peace in the midst of busy city life, a crowded and noisy environment, and most importantly, pressing daily routines and chores. Life can be especially stressful NOW when we are faced with huge uncertainties bought about by the greatest pandemic for the past 100 years.

Let us not forget that doctors work in one of the most stressful occupations. We face life, we face death, we face people, and we face long hours. Physician burnout is defined as a work-related syndrome involving emotional exhaustion, depersonalisation, and a sense of reduced personal accomplishment.

Surveys in the United States and United Kingdom have found burnout rate among doctors as high as 80%! A survey done in Hong Kong almost ten years ago showed that the rate for severe burnout was 30%. We believe that the current figure would be much higher now with escalating patient demand and workload! Serious and extreme burnout, if not dealt with properly, is associated with sudden death and suicide.

We also know that up to 80% of visits to doctors may have a stress-related component. Chronic stress is, therefore, not only an underlying factor in physician burnout. It also underlies many of the most chronic health challenges presented to physicians by their patients.

It is our belief that being healthy is not only about ‘physically not sick’. To possess a sound and peaceful mind and a sense of purpose in life are as crucial as health maintenance through physical exercise and taking nutritious food. We should not ignore the phenomenon that sleep problems are getting more prevalent, affecting general wellbeing and functioning.

The first author has been pursuing with a keen interest in various topics on mind-body medicine for the past 25 years. When faced with patients with various medical illness, I observed that the psychological aspect of care often plays an important part in the therapeutic outcome on top of the medical treatment or physical interventions we provide for them. Patients who are newly diagnosed with the critical illness have lots of fear and worries. Patients who have chronic illnesses easily become unmotivated to maintain their health.

I believe that as healthcare providers, we are doing our best to cater for the physical and psychological needs of our patients. However, wouldn’t it be wonderful if there can be some simple tools that can help patients and we can teach to patients to help them relieve stress without any side effects? To this end, sound healing is becoming accepted as one of the valid methods to alleviate stress, reduce burnout, improve sleep and improve general wellbeing.

HOW DOES SOUND HEALING WORK?

There are sounds all around us. The vibrational forces of sound are emitted from the movement or vibration of all matter. They manifest in a constant cacophony of sound waves, endlessly resonating in the universal sea of consciousness. These sounds are both audible and inaudible to the human senses. Regardless of our capacity to hear or feel sound waves, they manifest as cause and effect, not only to us as human beings but also to the wider world around us. Sound waves wash over us at every second of every minute and hour of every day and continue to vibrate endlessly.

A variety of instruments and tools, including the human voice, is used in sound healing. Positive intention through our dedication and devotion when working with these media is thought to play an important part in the overall healing effect. By transforming and replacing old and unhealthy energies with new and harmonious energies, sound healing can help to balance and harmonise us. Stress, tension and disease are manifested as a state of disharmony. Positive wellbeing will ensue when our natural resonance and harmony is restored. The human body is made up of 60% water on average. From the point of view of physics, the resonance created by sound can be transmitted to the water inside our body to cause vibration.

Sound healing works by:

1. Sympathetic resonance: Using a sound healing tool allows an area of imbalance to be brought back into balance through a “like vibration”, a vibration that matches the original frequency a given area most naturally wants to vibrate at. Through the projection of a sound tool’s pure, vibrational sounds, the waves go to the area of imbalance, the weak or dissonant frequency is transformed, and optimal resonance is restored.

2. Brainwave entrainment- Entrainment is the predisposition that two oscillating bodies have tendency to vibrate in harmony with one another. Entrainment occurs when two or more rhythmic cycles become synchronised.


4. Triggering the relaxation response to alleviate symptoms of chronic stress.
5. Releasing suppressed emotions associated with trauma from the past.

AUTONOMIC NERVOUS SYSTEM AND SOUND HEALING

The Autonomic Nervous System (ANS) is our body’s primary control centre. With its two main divisions, the sympathetic and the parasympathetic nervous system (or vagus), the ANS represents a superordinate control centre in the body. It controls and regulates all vital functions, including heart rate, blood pressure, respiratory rate, and other body system functions. Many diseases, including chronic diseases of physical and mental health, are diseases of the autonomic nervous system (ANS).

Polyvagal Theory is a new view of the ANS, going beyond the conventional view of the ANS having two branches: sympathetic and parasympathetic. Polyvagal Theory was developed by Dr Stephen Porges PhD, a research scientist, in the early 1990s. Dr Porges is a ‘Distinguished University Scientist’ at the Kinsey Institute at Indiana University Bloomington, USA. He is also Research Professor in the Department of Psychiatry at the University of North Carolina at Chapel Hill; Emeritus Professor of Psychiatry at the University of Illinois at Chicago and Emeritus Professor of Human Development at the University of Maryland, College Park.

His Polyvagal framework is now increasingly used by medical doctors, psychiatrists, psychotherapists, and in other therapeutic modalities. Polyvagal Theory is the understanding of how our body reacts to various challenges. Our reactions are based on the evolution of our autonomic nervous system. During our evolutionary history as vertebrates, the autonomic nervous system has changed. As it changed, it created different circuits.

In Polyvagal Theory there are three circuits, and they function in a hierarchy (Fig. 1)

1. social engagement corresponding to the ventral vagal circuit (supra-diaphragmatic vagus)
2. fight/flight corresponding to the sympathetic nervous system
3. freeze/shutdown corresponding to the dorsal vagal circuit (sub-diaphragmatic vagus)

THE VENTRAL VAGAL CIRCUIT

The newer circuits can inhibit older circuits. The newest circuit is the circuit of social interaction which is linked to the uniquely mammalian vagal pathway the ventral vagal circuit. The ventral vagal circuit is the nerve going from the brain stem to the heart (CN X). The vagus nerve is linked in the brainstem to the nerves that regulate the muscles in the face and head which are involved in social engagement, including CN V (trigeminal nerve) CN VII (facial nerve). These are the muscles of vocalisation, listening, facial expressivity and gesture.

The ventral vagal circuit is the co-regulatory, interactive regulation of the autonomic state that enables our bodies to be in states that support growth, health and restoration. When that system does not work properly, we see the behaviours and the symptoms associated with physical and mental health issues. Improved flexibility and functioning of ventral vagus nerve creates a VAGAL BRAKE on dysfunctions in the spinal sympathetic nervous circuit. Such dysfunction can create a chronic mobilised state of fight/flight. Dysfunction of the dorsal vagus nervous circuit is associated with the chronic immobilised state of freeze/shutdown with fear.

Dysfunction in the nerves of the ventral vagus circuit is an underlying cause of many life impairing physiological and behavioural conditions. Learning how to correct this dysfunction and how to improve the functioning of the ventral vagal circuit is a quick, cheap and effective medical intervention. This approach can eliminate the adverse effects of chronic stress arising from overstimulation of spinal sympathetic circuit. It can also eliminate the adverse effects of the shutdown and depressive behaviour arising from hyperactivity in the dorsal vagus circuit. Positive effects are cumulative. The ANS becomes more resilient each time we improve the flexibility and functioning of the ventral vagus circuit.

FROM THEORY TO PRACTICE

We have found that to successfully integrate Polyvagal theory into clinical practice; it is necessary to have a quick, cheap and reliable method of measuring the ANS.

As the heart is controlled directly by the sympathetic and parasympathetic nervous system, it acts as an effector organ to measure the autonomic nervous system. The sympathetic and parasympathetic nervous systems register and process internal and external stimuli. They initiate the proper reactions to optimally prepare the organism according to the needs of the moment (e.g. energy supply in times of sudden danger). A malfunctioning ANS has an overactive sympathetic and hypoactive parasympathetic nervous system. Such state inevitably leads to a physiological change in the heart’s excitation pattern. Thus, the Heart Rate Variability (HRV) - the beat-to-beat interval will be changed accordingly. This change is measurable. HRV is determined by the measurement and evaluation of the RR intervals (time period between successive heartbeats) There are commercially available software programs that allow measurement of HRV and provide analysis of the functioning of sympathetic and dorsal and ventral parasympathetic systems.
The international Sound Healing Academy has worked for three years to determine the effect of sound healing instruments and techniques on HRV, and therefore on the functioning of the ANS. With specific sound healing interventions, it is possible to improve the regulation of the ANS as shown by improved HRV and ventral parasympathetic system functioning.

PERSONAL OBSERVATIONS WITH SOUND HEALING

The first author has an avid interest in sound healing, first as a tool for personal development and relaxation; and then subsequently as a tool to help my family and friends with various issues (Fig. 2 & 3). For myself, I find that the sound emitted by various sound instruments to be very soothing (Fig. 4) and can help myself to focus on the moment by drawing my attention away from various mundane daily matters. It also facilitates me going into a meditative state more easily.

Below is some of the anecdotal experience I had and is by no means suggesting that sound therapy is the definitive cause for the improvement in each case. Medical assessment and management is essential and cannot be bypassed.

My wife used to have chronic lower back pain requiring analgesics from time to time. I tried sound therapy for her, and after several sessions, her pain is 90% relieved, and she has not taken analgesics for the past few years.

A friend of my wife used to have chronic insomnia. She was seen by a psychiatrist and could only sleep for 1-2 hours at night even with adding to 5 medications for one year. She was exhausted when I first met her. After several sessions and my instruction to her to practice playing a tuning fork daily for practice, I was so overjoyed to hear that she could sleep for 5-6 hours in a row. Over the subsequent three months, her doctor has successfully reduced her medications to one item only. After one year, she was still well maintained on only one medication and was sleeping a few hours per night and in a brighter mood.

A friend of mine had chronic fatigue syndrome, rendering her bed-bound. She could barely support standing for 3 minutes alone at the worst of time. I diligently performed the therapy for her over ten sessions. I was so excited that she had marked improvement in her exercise tolerance progressively. She also told me that her chronic insomnia problem had markedly improved and the psychiatrist tailed down her medications gradually.

One ‘side-effect’ I get from performing the sessions for others is that I found that I slept very deeply on the same night that I performed the therapy. Also, I am generally more relaxed and can maintain working long hours easily without fatigue compared to before I took up this hobby.
THE NEW ERA OF HOLISTIC MEDICINE

The visionary Edgar Cayce once predicted 100 years ago that ‘Sound will be the medicine of the future’. We are still far away from the stage where it is integrated as a mainstream therapy. Nevertheless, the blooming of various sound spas and sound baths especially in the West and now in Hong Kong signify that, at least for some people, the sound is appealing to them as a means to de-stress.

We believe that the Polyvagal Theory is a good scientific foundation whereby the effect on the ANS can be measured and hence quantified. We eagerly await results from a rigorous scientific study on the effect on this intervention. Even without RCTs, as a complementary therapy, sound therapy has great potential as a simple self-help therapy which can engage clients and as a ‘feel-good’ quick fix without side effects. As time goes by, we hope that more and more people would be opening up to experience its vast benefits.

References

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Indications: Topical treatment of onychomycosis (tinea unguium) of the toenails due to Trichophyton rubrum and Trichophyton mentagrophytes.

Dosage: Apply to affected toenails once daily for 48 weeks. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.

Contraindications: Hypersensitivity to efinaconazole or excipients or component of the container.

Precautions: JUBLIA is for external use only and is not for ophthalmic, oral, or intravaginal use. Flammable, avoid use near heat or open flame. Drug interactions: In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

Adverse Reactions: The most common adverse reactions (incidence >1%) were ingrown toenails, application site dermatitis, application site vesicles, and application site pain.

Before prescribing, please consult full prescribing information which is available upon request.

References

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(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

The Hong Kong Ophthalmological Society

Objectives:
This course aims to provide an overview and update on the diagnosis and management of common and important eye diseases. After attending the course, attendees will learn how to deal with common ophthalmic conditions and when to refer patients to ophthalmologists.

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<th>Speakers</th>
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<td>19 Aug, 2020</td>
<td>Cataract and Cataract Surgery Update</td>
<td>Dr. CHAN Chung Yan, Tommy FHKAM (Ophthalmology)</td>
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<td>Refractive Errors, Presbyopia and Refractive Surgeries</td>
<td>Dr. NG Lap Ki, Alex FHKAM (Ophthalmology)</td>
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<td>26 Aug, 2020</td>
<td>Corneal and External Eye Diseases</td>
<td>Dr. FAN Ching Yim, Michelle FHKAM (Ophthalmology)</td>
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<td>Glaucoma and Glaucoma Surgery Update</td>
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<td>Dr. HO Wing Lau FHKAM (Ophthalmology)</td>
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<td>Squint, Paediatric Ophthalmology</td>
<td>Dr. YUENG Chun Chun, Jane FHKAM (Ophthalmology)</td>
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<td>9 Sep, 2020</td>
<td>Update in Orbital Diseases and Oculoplastic Surgery</td>
<td>Dr. LI Chi Lai FHKAM (Ophthalmology)</td>
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<td>Red Eyes, Ocular Trauma and Emergencies</td>
<td>Dr. CHOY Nga Kwan, Bonnie FHKAM (Ophthalmology)</td>
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<td>16 Sep, 2020</td>
<td>Retinal Detachment and Diabetic Retinopathy</td>
<td>Dr. LAI Hiu Ping, Frank FHKAM (Ophthalmology)</td>
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<td>Common Macular Diseases and. Treatment</td>
<td>Dr. LUK Oi Jing, Fiona FHKAM (Ophthalmology)</td>
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<td>23 Sep, 2020</td>
<td>Ophthalmic Imaging</td>
<td>Dr. MOHAMED Shaheeda FHKAM (Ophthalmology)</td>
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<td>Use of Laser in Ophthalmology</td>
<td>Dr. YUEN Shi Yin, Nancy FHKAM (Ophthalmology)</td>
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Date: 19, 26 August & 2, 9, 16, 23 September, 2020 (Wednesday)
Time: 7:00 p.m. – 8:30 p.m.
Course Feature: Video lectures (with Q&A platform)
Language Media: Cantonese (Supplemented with English)
Course Fee: HK$1,000 (6 sessions)
Certificate: Awarded to participants with a minimum attendance of 70%
Enquiry: The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: vienna.lam@fmshk.org

CME / CNE / CPD Accreditation in application
Online application from website: http://www.fmshk.org
# Medical Diary of August

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<th>Sunday</th>
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<td>Evaluation of Antidepressants Efficacy and Individualized Treatment Approach (Online Symposium)</td>
<td>Certificate Course on Complaint Management 2020 (Video Lectures)</td>
<td>Facebook Live: Updates on IPV conference 2020 and Male HPV cancer prevention</td>
<td>Certificate Course on Complaint Management 2020 (Video Lectures)</td>
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- Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)
- Certificate Course on Complaint Management 2020 (Video Lectures)
- Facebook Live: Certificate Course in Allergy 2020 (Video Lectures)
- Facebook Live: Drive and the Management of Premature Ejaculation
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<th>Date / Time</th>
<th>Function</th>
<th>Enquiry / Remarks</th>
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| 1 SAT      | Facebook Live  
1. Sexuality in COVID-19 Era  
2. Unmet Need on the Management of Erectile Dysfunction and the Role of Avanafil  
Organiser: Hong Kong Medical Association; Speaker: Prof Emmanuele A. JANNINI  
HKMA CME Department  
2527 8285  
1 CME Point | HKMA CME Department  
2527 8285  
1 CME Point |
| 3 MON      | Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr WONG Wai-shan | Ms. Vienna LAM  
Tel: 2527 8898 |
| 4 TUE      | Evaluation of Antidepressants Efficacy and Individualized Treatment Approach (Online Symposium)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Prof. Michael LÄNDGREBE  
Facebook Live  
Abdominal Pain Management in Children  
Organiser: Hong Kong Medical Association; Speaker: Dr Philip Chak-on SHAM | HKMA CME Department  
2527 8285  
1 CME Point |
| 5 WED      | Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Wing-chi CHAN | Ms. Vienna LAM  
Tel: 2527 8898 |
| 6 THU      | Certificate Course in Allergy 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Marco Hok-kung HO | Ms. Vienna LAM  
Tel: 2527 8898 |
| 7 FRI      | Certificate Course on Complaint Management 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Ms Suk-chong LÜNG, Ms Asha SHARMA, Ms Janice DAO | Ms. Vienna LAM  
Tel: 2527 8898 |
| 10 MON     | Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Anita KAN | Ms. Vienna LAM  
Tel: 2527 8898 |
| 12 WED     | The Hong Kong Neurosurgical Society Monthly Academic Meeting –COVID-19 and Neurosurgery  
Organizer: Hong Kong Neurosurgical Society; Speaker(s): Dr CHEUNG Yuk Hong, Eric Chairman: Dr CHEUNG Fung-ching; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting  
Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Yat-bong YEUNG | 1.5 points  
College of Surgeons of Hong Kong  
Name: Dr Calvin MAK  
Tel: 2959 6456  
Fax. No.: 2965 4061  
Ms. Vienna LAM  
Tel: 2527 8898 |
| 14 FRI     | Facebook Live  
Updates on IPV conference 2020 and Male HPV cancer prevention  
Organiser: Hong Kong Medical Association; Speaker: Dr Tin-yau WONG  
Certificate Course on Complaint Management 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Kai-ming CHOW | HKMA CME Department  
2527 8285  
1 CME Point |
| 17 MON     | Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Chris Tsun-leeung CHAN | Ms. Vienna LAM  
Tel: 2527 8898 |
| 21 FRI     | Certificate Course on Complaint Management 2020 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Kim-lian ONG | Ms. Vienna LAM  
Tel: 2527 8898 |
Answers: 

1. The adrenal glands appear as a pair of V-shaped structures superior and anteromedial to the kidneys on CT scan. The adrenal limbs are thin in calibre (<5mm) and any focal or diffuse thickening is considered abnormal.

2. A small nodule is shown at the lateral limb of the left adrenal gland. The risk of malignancy of an incidental adrenal nodule/ mass is extremely low, reported being 0.0007% in a meta-analysis of 1,040 lesions by Sullivan and colleagues in BMJ in 2018. For comparison, the risk of malignancy of incidental breast, renal and colon masses are quoted as 42%, 25% and 17% respectively in the same paper.

3. The low attenuation of the nodule indicates the presence of fat, favouring a benign lesion such as adenoma or myelolipoma. If the lesion shows no definite fat attenuation, a dedicated triphasic adrenal CT can be performed to calculate the washout ratio to differentiate between adenomas and other lesions.

4. Catheter-guided adrenal venous sampling can be performed at an interventional radiology unit. In this procedure, blood samples are taken from bilateral adrenal veins, and the peripheral venous blood and cortisol and aldosterone levels are measured. Normalised aldosterone levels and laterisation indices (LI) can then be calculated. A LI greater than four is generally considered sufficient evidence for a culprit functioning adrenal adenoma. Contralateral gland suppression is advocated by some authors as a confirmatory test.

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References:

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EXPERT INTERVIEW

Prof. Liam O’Mahony
Departments of Medicine and Microbiology
APC Microbiome Ireland
National University of Ireland
Cork, Ireland

Read the full interview at:
https://hongkong.wyethnutritionsc.org/expert-interview

The Latest Evidence Linking Early Nutrition and Childhood Allergy Outcomes

What are the mechanisms that link the diet, microbiome and metabolism to the development of the immune system?

Does diversity of the diet play a role in protecting against allergies?

Practical tips for optimising the lifelong health of infants?

Key Points from Prof. O’Mahony

- Microbes in the gut metabolise dietary fibre to produce short chain fatty acids (SCFA), which program and modulate both the innate and adaptive immune system.

- Similarly, human milk oligosaccharides (HMOs) are preferentially utilised by bifidobacteria in the infant’s gut, and studies show that certain HMO profiles may offer protection against food allergies.

- A diverse diet high in fibre, fermented foods and omega-3 fatty acids is recommended to safeguard against childhood allergies and help support the development of a healthy, optimised microbiome.
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