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The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

Looking Ahead to the Expansion Roles of Pharmacists to Improve the Healthcare System in Hong Kong

The number of pharmacy graduates from the Chinese University of Hong Kong and the University of Hong Kong has increased to over 85 every year. We should examine how we can utilize these pharmacists for the benefit of our patients and healthcare system in Hong Kong. Globally, there have been significant changes in the role of pharmacists in healthcare. Their role evolved from filling prescriptions and verifying the correct dose, to diabetes education, hypertension screening, checking for drug interactions, and assisting in vaccinations. These new challenges have resulted in the need for pharmacists to acquire new skills and services. Our local pharmacy graduates are equipped with more clinical skills than they used to, but are not always allowed to practice their skills to the fullest. With the ageing population, there is the need for more clinics and hospitals and increased demand for good pharmaceutical care.

Our Public Hospital should create more posts for Clinical pharmacists and Ward pharmacists to conduct medication review upon admission, during hospital stay and upon leaving the hospitals. This can relieve the workload of the doctors and nurses and reduce the number of polypharmacy, drug interactions and optimize medication therapy for the patients. They can also focus on care transitions. Transitioning patients from one care setting to another is a vulnerable time, which requires improvement. Community and hospital pharmacists are valuable allies for reducing the risks associated with transitions, especially those back to the nursing home. They can actively be involved in transition care.

With community pharmacies being the most accessible primary healthcare destinations, there is a tremendous opportunity to deliver great health outcomes for the citizens of Hong Kong.
-Elderly residents in old aged homes are polypharmacy and are more likely to suffer from adverse effects of medicines which can lead to otherwise preventable hospital admissions. As medicine experts, community pharmacists have a big contribution to make in improving medicines management in OAHs. Medication reviews, medication reconciliation and medicines use reviews play an important role to reduce polypharmacy, adverse drug reactions and improving adherence, meaning to improve the quality of life for the elderly residents and reduce hospitalizations and cost of the healthcare system
-Home medicine reviews are also a service pharmacists can provide, which involves a pharmacist, referred by a GP, to visit a patient in their home and review their medications. This service has already been applied in many countries including Canada, US, and Australia.
-Immunisations and vaccinations: Flu and shingles vaccinations are currently available in guardian pharmacies in Singapore. Pharmacists will assess for allergies before the nurse administers the vaccination. Other countries like Australia and US have recently introduced training to allow for pharmacists to vaccinate. This can be an opportunity for pharmacists in the near future.
- Chronic disease management & primary prevention
Pharmacists can provide specialized care for those at high risk of developing diseases such as diabetics and cardiovascular disease. Such practices are already in place, which include lipid screening, blood glucose testing, and blood pressure checking. There are many pharmaceutical services developed worldwide. In the USA, Medication Therapy Review(MTR) by pharmacists is widely adopted. The medication therapy review is a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them.

All the above services should be developed in Hong Kong and the leaders of the universities, pharmaceutical societies,unions must negotiate with the government and insurance company to obtain remuneration for providing these services.

Pharmacist can also play an important role in Antibiotic Stewardship programme in healthcare settings. Current scientific literature emphasizes the need to reduce the use of inappropriate antimicrobials in all health care settings due to antimicrobial resistance. According to the World Health Organization: Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. The Centers for Disease Control and Prevention (CDC) identified that 20%–50% of all antibiotics prescribed in acute care hospitals are either unnecessary or inappropriate. In 2005, the Joint Commission developed the antimicrobial stewardship standard for hospitals, critical access hospitals, nursing care centers, ambulatory care organizations, and office-based surgery practices to slow the emergence of antibiotic-resistant bacteria, detect resistant strains, preserve the efficacy of existing antibiotics, and prevent the spread of resistant infections. In the article on page 127 of this issue, MAK Chun Yiu and CHU Jody wrote about the Antibiotic Stewardship Program Focusing on Ciprofloxacin. Ciprofloxacin is the only orally active agent with good efficacy against Pseudomonas aeruginosa (P. aeruginosa), but resistance from this pathogen has been widely reported in surveillance studies. Implementing Antibiotic Stewardship Programme (ASP) and drug use evaluation (DUE) can optimize the use of ciprofloxacin and other antibiotics and preserve their distinct property. The article also discussed about the important elements for a successful Antibiotic Stewardship Programme.

CHOW, Cheuk Hin; NGAI, Chun Hin; LI, Lok Him; EWIG, Celeste LY wrote about the use of oral vitamin D in the pediatric population to prevent or correct inadequate levels resulting from conditions contributing to low vitamin D serum levels on page 134. It also reported some studies on additional benefits of vitamin D beyond its role in bone health. By reviewing the current clinical recommendations alongside other potential benefits of vitamin D, pharmacists may better identify patients at risk for vitamin D deficiency, recommend sufficient supplementation corresponding with their vitamin D levels and understand the role of vitamin D in other novel indications.

On page 144, ALBÉRT, Anna Maria; CHEUNG, Tsz Yan; CHEUNG, Hon Yeung wrote about the effect of Zika Viral Transmission on Human Health. Zika virus disease is caused by a virus transmitted primarily by Aedes mosquitoes. People with Zika virus disease can have symptoms including mild fever, skin rash, conjunctivitis, muscle and joint pain, malaise or headache. Zika can be passed from a pregnant woman to her fetus. Infection during pregnancy can cause certain birth defects. There is scientific consensus that Zika virus is a cause of microcephaly and Guillain-Barré syndrome. There is no vaccine or medicine for Zika, and the safest way to avoid infection is to protect oneself against mosquitos bites.

Last but not the least, Mr Lot Chan, Chief Pharmacist and Chairman of the Hong Kong Pharmacy Conference 2017 invited all of you to participate in the upcoming conference on 18-19 February. The programme is packed with the latest innovations and advancements in the field to inspire you. I wish all of you good health, happiness and success in the year of the Rooster!

Cheng Mary Catherine
Managing Editor
14 January 2017

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Prepared by Alfie Chan, Kelvin Cheng, Angus Choi, Bryan Kan, Anders Kwan, William Kwan, Karpio Marlise Lam, Miriam Leung, Jeffrey Man, Nicole Tam, Ivy Tsang, Sally Tsang, Hercules Tse, Annie Tsoi

Adjunctive Azithromycin Reduces Risk of Infection for Caesarean Delivery

Date: September 29, 2016

More than 60% of caesarean sections are non-elective, meaning that they are unscheduled during labour, after membrane rupture, or for maternal or foetal emergencies. Up to 12% of women undergoing non-elective caesarean delivery suffered from postoperative infections, including endometritis and wound infection, despite routine use of standard antibiotic prophylaxis. Given the suggestion from prior studies, a study has been conducted to assess the benefits of adjuvant azithromycin to non-elective caesarean section.

The study was a double-blind, pragmatic, randomized clinical trial. It recruited 2013 women from 14 hospitals in the United States. The female subjects had had a singleton pregnancy with a gestation of 24 weeks or more, and were undergoing non-elective caesarean delivery during labour or after membrane rupture. On top of the standard antibiotic prophylaxis, 1019 of them were randomly assigned to receive 500mg of intravenous azithromycin, and 994 received placebo. The study observed a composite of endometritis, wound infection, or other infection taking place within 6 weeks as the primary outcome. Secondary neonatal and maternal outcomes were included.

The azithromycin group showed a significantly lower rate of endometritis (3.8% vs. 6.1%, P=0.02) and wound infection (2.4% vs. 6.6%, P=0.03). There was no significant between-group difference in the secondary neonatal composite outcome that included neonatal death and serious neonatal complications (14.3% vs. 13.6%, P=0.63).

The study concluded that an extended-spectrum prophylaxis with the adjuvant azithromycin was effective in reducing the risk of postoperative infection with no evidence of neonatal harm.

Source: www.nejm.org

Ticagrelor is Not Superior to Clopidogrel in Symptomatic Peripheral Artery Disease

Date: November 13, 2016

Peripheral artery disease is viewed as a manifestation of systemic atherosclerosis with associated adverse cardiovascular and limb events. With data from previous trials, patients receiving clopidogrel monotherapy had a lower risk of cardiovascular events than those receiving aspirin. Lately, ticagrelor was used in Peripheral Artery Disease (EUCLID) trial to test the hypothesis that monotherapy with ticagrelor would be superior to that with clopidogrel in preventing cardiovascular death, myocardial infarction, or ischemic stroke in patients with symptomatic peripheral artery disease.

A double-blind, event-driven trial was conducted and 13,885 patients with symptomatic peripheral artery disease were randomly assigned to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). While the primary efficacy end point was a composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke, the primary safety end point was major bleeding.

It was found that the primary efficacy end point occurred in 751 of 6930 patients (10.8%) for patients receiving ticagrelor and 740 of 6955 (10.6%) for patients receiving clopidogrel. Major bleeding occurred in 1.6% of patients in both group. In conclusion, patients with symptomatic peripheral artery disease using monotherapy with ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events, and both drug was associated with similar rates of major bleeding.

Source: www.nejm.org

Short-term Risk of Venous Thromboembolism with Testosterone Treatment

Date: November 30, 2016

Testosterone is solely indicated for pathological hypogonadism. However, it is heavily prescribed for unjustified causes including sexual dysfunction and decreased energy.

Recent studies have found the association between testosterone and cardiovascular events. To confirm the risk of testosterone treatment over time, a population based case-control study was carried out. It has analysed more than 2.2 million men aged 20 to 89 in the UK Clinical Practice Research Datalink (CRPD) between 2001 and 2013. The research has applied a validated algorithm for venous thromboembolism to identify first occurrence (sensitivity: 92.6% & specificity: 98.6%). The main outcome of the study is the rate ratios of venous thromboembolism in association with current testosterone treatment compared with no treatment.

The adjusted rate ratio of venous thromboembolism was 1.25 (95% CI: 0.94 to 1.66) for current versus no testosterone treatment. In the first six months of testosterone treatment, the rate ratio of venous thromboembolism was 1.63 (1.12 to 2.37). The rate ratio was 1.00 (0.68 to 1.47) after six month of treatment and was 0.68 (0.43 to 1.07) as treatment ceased. Increased rate ratios within the first six months of treatment were observed in all strata, regardless of the presence of pathological hypogonadism and the pre-existing risk factors.

Starting testosterone treatment was associated with an increased risk of venous thromboembolism, which peaked within six months and declined thereafter.

Source: www.bmj.com

Sublingual Immunotherapy Improved Clinical Outcome in Treating House Dust Mite Induced Allergic Rhinitis

Date: December 1, 2016

House dust mites (HDM) are common inhaling allergens, accounting for more than 50% of the allergic cases. Apart from taking antihistamines to relieve symptoms, sublingual immunotherapy (SLIT) by giving oral tablets of the allergen extract was found to be clinically beneficial to rhinitis patients via modulating the type 1 hypersensitivity pathway. Previous SLIT trials on different allergens have demonstrated that that immunomodulation effect could persist after the discontinuation of the treatment.

In a phase III randomized double-blind study (NCT01700192), the efficacy of HDM SLIT tablets (MK8237, Merck & Co.) in treating against house dust mites-induced allergic rhinitis was investigated with N = 1482. The treatment group participants were given with MK8237 once daily, which consists of 15 µg group 1 HDM allergens and 15 µg group 2 HDM allergens.

Compared with the placebo group, the total combined rhinitis score (TCRS), rhinitis DDS, and TCS scores were significantly reduced by 17% (95% CI, 10% to 25%; $p < 0.001$), 16% (95% CI, 7% to 24%; $p < 0.001$), 17% (95% CI, 4% to 25%; $p < 0.001$) respectively in patients treated with MK8237. The rhinitis DMS score was not significantly different ($p = 0.15$). A rise in anti-house dust mite IgE levels was found at week 4 in the treatment arm, with a gradual decrease at the end of the study. In contrast, anti-house dust mite IgG4 levels increased consistently and peaked at the end of the trial. This suggested that MK8237 may suppress the type 1 hypersensitivity in HDM-induced AR through upregulating the Treg cells activity.

The most common reported treatment-related adverse events are throat irritation (67%), oral pruritus (62%) and ear pruritus (51%). Three participants took epinephrine for the adverse events related to treatment and one participant had non-serious systemic allergic reactions related to MK8237.

The above results demonstrated that MK8237 was well tolerated in allergic rhinitis patients and met the clinically relevant standards by FDA of having greater than 15% improvements in TCRS compared with placebo treatment.

Source: www.jacionline.org

Systematic Review and Meta-analysis Support the Role of Alpha Blockers for Treatment of Ureteric Stones

Date: December 1, 2016

Alpha blockers have been shown to be efficacious in the initial treatment of patients with newly diagnosed and uncomplicated ureteric stones by showing a higher risk of stone passage. However, most supporting data came from small, single center and low quality studies. Therefore, a large confirmatory trial involving 1100 patients with ureteric stones has been conducted in the United Kingdom.

Randomized controlled trials comparing alpha blockers (tamsulosin, alfuzosin, doxazosin, naftopidil, solidosin, terazosin) with placebo or control for treatment of ureteric stones were investigated. Only those trials in which alpha blockers were used as the main treatment were included. The primary outcome was the proportion of patients who passed their stone. The secondary outcomes were the time of passage, the number of pain episodes and the proportions of patients who underwent surgical intervention, required admission to hospital, and experienced a serious adverse event. Specific adverse events like headache and fatigue were also examined.

From the 55 randomized control trials, alpha blockers were shown to facilitate the passage of ureteric stones (risk ratio 1.49, 95% CI: 1.39-1.61), with their effect independent of stone location. While alpha blockers did not seem to be beneficial to patients with smaller ureteric stones (risk ratio 1.19, 95% CI: 1.00-1.48), they led to a 57% higher risk of stone passage among patients with larger stones (risk ratio 1.57, 95% CI: 1.17-2.27). Patients received alpha blockers also had significantly shorter times to stone passage, fewer episodes of pain, lower risks of surgical intervention and lower risks of admission to hospital. Concerning the risk of a serious adverse event, it was similar between treatment and control group (risk ratio 1.49, 95% CI: 0.24-9.35).

The above results showed that alpha blockers seem efficacious in the treatment of patients with ureteric stones, and are of particular benefit in patients with larger ureteric stones. The current guidelines advocating the role of alpha blockers in patients with ureteric stones were supported.

Source: www.bmj.com

Ocrelizumab is Effective in Treating Primary Progressive Multiple Sclerosis

Date: December 21, 2016

An evolving understanding of the immunopathogenesis of multiple sclerosis suggests that depleting B cells could be useful for treatment. A phase 3, randomized, parallel-group, double-blind, placebo-controlled trial (ORATORIO) investigated the efficacy and safety of ocrelizumab, a humanized monoclonal antibody that selectively depletes CD20-expressing B cells, in patients with primary progressive multiple sclerosis. 732 patients with primary progressive multiple sclerosis were randomly assigned in a 2:1 ratio to receive intravenous ocrelizumab (600 mg) or placebo every 24 weeks for at least 120 weeks and until a prespecified number of confirmed disability progression events had occurred.

The primary end point was the percentage of patients with 12-week confirmed disability and was measured to be 32.9% with ocrelizumab versus 39.3% with placebo (P=0.03). The percentage of patients with 24-week confirmed disability progression was lower with ocrelizumab than with placebo (29.6% vs 35.7%, P=0.04). By week 120, performance on the timed 25-foot walk worsen less with ocrelizumab than with placebo (38.9% vs 55.1%, P=0.04). The mean change in total volume of brain lesions was -3.4% with ocrelizumab and 7.4% with placebo (P<0.001); and the percentage of brain-volume loss was 0.90% with ocrelizumab versus 1.09% with placebo (P=0.02). No significant difference was observed between the rates of serious adverse events and serious infections.

The study concluded that among patients with primary progressive multiple sclerosis, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo. Nonetheless, extended observation is required to determine the long-term safety and efficacy of ocrelizumab.

Source: www.nejm.org

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Antibiotic Stewardship Programme: Focusing on Ciprofloxacin

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ABSTRACT

Antibiotic resistance limits the choice of agents against microbes, and such phenomenon has been reflected by the changes of recommendations in treatment guidelines. World Health Organization's (WHO) Global Report on Surveillance of Antimicrobial Resistance issued an alert that resistance had occurred in even "last resort" antibiotics all over the world in 2014 and urged the preservation of our weapons against superbug. Ciprofloxacin is one of the agents facing the resistance problem. Ciprofloxacin is the only orally active agent with good efficacy against *Pseudomonas aeruginosa (P. aeruginosa)*, but resistance from this pathogen has been widely reported in surveillance studies. Implementing Antibiotic Stewardship Programme (ASP) and drug use evaluation (DUE) can optimize the use of ciprofloxacin and other antibiotics and preserve their distinct property. Increase in susceptibility of *P. aeruginosa* to ciprofloxacin as a result of ASP has been demonstrated in various studies previously. Other advantages of ASP include a reduction of antimicrobial use while not compromising patient outcome. In this review, previous ASP and DUE studies of ciprofloxacin will be discussed with their pros and cons, followed by the framework for future local ASP development. The importance of education, surveillance, approval system, IT development and managerial involvement will also be highlighted.

Keywords: *ciprofloxacin, quinolones, antibiotic resistance, pseudomonas aeruginosa, antibiotic stewardship programme, drug use evaluation*

INTRODUCTION

The World Health Organization (WHO) recognised antibiotic resistance as a major threat to public health at a global level in the past two decades. The Global Strategy for Containment of Antimicrobial Resistance was first published in 2001 by WHO as part of the range of initiatives for tackling antimicrobial resistance.[1] In April 2014, WHO's Global Report on Surveillance of Antimicrobial Resistance revealed that resistance had occurred in even "last resort" antibiotics all over the world and once again urged the importance of appropriate utilization of antimicrobial agents.[2] Indeed, resistance problem has already led to changes in clinical management guidelines.

Antibiotic Stewardship Programme (ASP) has been implemented in many regions around the world including Hong Kong. Hospital Authority (HA) in Hong Kong has implemented ASP since 1999 when the first edition of Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT) guideline was published.[3] Drug use evaluation (DUE) or audit is one of the useful measures in ASP to assess the appropriateness of antibiotic usage. In this review, ciprofloxacin, a quinolone class antibiotic, is used as an example to illustrate the potential benefits of ASP and DUEs. Barriers to implementing DUE and future directions of ASP are also discussed.

CLINICAL VALUE OF CIPROFLOXACIN IN TREATING PSEUDOMONAS AERUGINOSA RELATED INFECTIONS

Ciprofloxacin is an antimicrobial agent classified as a second generation quinolone. Quinolones exhibit antibacterial activity by inhibiting DNA synthesis in bacteria[4]. Besides its coverage of aerobic gram-negative and atypical bacteria,[4, 5] ciprofloxacin also has an important clinical value in fighting against *Pseudomonas aeruginosa (P. aeruginosa*).[6]

Ciprofloxacin is the only antipseudomonal agent that can be administered in oral route with good efficacy (levofloxacin has a lower efficacy against *P. aeruginosa*), making it an attractive drug of choice for patients requiring long term oral antibiotic treatment. Therefore, it is crucial to optimize the use of ciprofloxacin for the preservation of its distinctive and favorable feature in clinical practice given the increasing resistance trend of *P. aeruginosa* reported in various literatures.[7-11]

P. aeruginosa is a gram-negative rod bacteria which is commonly found from soil and water.[12] *P. aeruginosa* raises much concern given its intrinsic resistance property and the high mortality rate associated with *P. aeruginosa*-related infection.[12, 13] Literature suggested the rate of resistance in *P. aeruginosa* was around 10-20% in Asia-Pacific region.[14-16] *P. aeruginosa* has been identified as the cause of severe nosocomial infections. In fact, *P. aeruginosa* was the second most common cause for nosocomial pneumonia[17]

and the third most common intensive care unit (ICU) isolate in the US.[18] Data from a local hospital in Hong Kong in 2011 indicated that *P. aeruginosa* was the top isolate from respiratory specimens in non-ICU ward and the second highest for ICU ward.[19]

Relationship between Ciprofloxacin Use and *P. aeruginosa* Resistance Rate

Evidence from the literature has repeatedly demonstrated the relationship between increasing use of antimicrobial agents and a higher rate of resistance.[20-23] A national surveillance study in the US in 1990s and 2 studies in France in 1990s and early 2000s found a significant association between increasing rate of ciprofloxacin resistance for *P. aeruginosa* and increasing use of quinolones.[11, 24, 25] Similar observation was seen in Japan and Taiwan as well.[26,27] In fact, quinolones use was found to be a risk factor for the colonization as well as infection of *P. aeruginosa*.[11]

On the other hand, studies in individual hospital level concluded that reduction of the use of ciprofloxacin could lead to decrease in resistance of *P. aeruginosa*. After restriction of ciprofloxacin use in ICU of a tertiary care US teaching hospital in an interrupted time series analysis, a significant 13.7% reduction in ciprofloxacin-resistant *P. aeruginosa* isolates was observed.[28]

ANTIBIOTIC STEWARDSHIP PROGRAMME (ASP) and DRUG USE EVALUATION (DUE)

Antibiotic resistance has been associated with an increase in mortality of the patients, length of hospital stay and healthcare cost.[29] Implementation of ASP is a measure implemented to tackle this problem. ASP is supported by various healthcare authority bodies including WHO, IDSA and Centers for Disease Control and Prevention (CDC).[3] It involves a multidisciplinary, programmatic, prospective and interventional approach. The main components of antimicrobial stewardship involve the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.[3, 30]

Drug use evaluation (DUE) or drug utilization review is a powerful tool under ASP, it is defined by Academy of Managed Care Pharmacy (AMCP) as a structured review of medication prescriptions against a set of criteria to assess the appropriateness of drug use.[31] Patient's medical and drug history, and clinical outcomes are taken into consideration in the process.[31] The goals of antibiotic DUE are to reduce adverse effect, improve treatment effectiveness, prevent unnecessary or inappropriate use of antibiotics and hence reduce bacterial resistance.[31] Local protocols and international guidelines are used to assess the appropriateness in prescriptions. Potential benefits of ASP and DUE are listed below:

1. Reduction of antimicrobial consumption
2. Increasing bacterial susceptibility
3. Optimizing treatment outcome with shorter length of stay in hospital and re-infection rate[32]
4. Increasing appropriateness of antimicrobial prescription

PREVIOUS DUE CONDUCTED ON CIPROFLOXACIN

Many DUEs **(Table 1)** on ciprofloxacin have been carried out previously. Speirs *et al.* demonstrated that 14 out of 35 patients (40%) receiving ciprofloxacin in his audit had been classified as non-justified in 1992.[33] Hecker *et al*. conducted a prospective observational study in a university-affiliated hospital in 2003 to monitor the 153 antibiotic regimens prescribed for 129 patients, with 1941 days of antimicrobial therapy, in a 2-week period. 36 (23.5%) out of 153 regimens were unnecessary while 54 regimens (35.3%) were partially unnecessary. In terms of treatment length, 576 (30%) of all 1941 days of therapy were deemed unnecessary.[34] Common misuses identified include longer duration than recommended, second-line therapy taken as first-line, and administration for noninfectious or nonbacterial syndromes.[34, 35]

DUE is often useful in increasing the appropriateness of prescription along with other interventions. In 1995, a pre- and post-intervention DUE (total 115 patients in pre-intervention phase; 126 patients in post-intervention phase) carried out by Hammerman et al. showed significant improvement in appropriate ciprofloxacin use, in which unjustified use decreased from 31% to 13% ($p<0.005$).[36] Significant increase in justified use (65% to 85%, $p<0.025$) of the drug was also observed in UTI treatment (total 34 and 52 UTI treatment cases in pre- and post-intervention phase respectively).[36] Education materials were designed based on the data collected in the pre-intervention DUE. Interventions included meetings initiated by infectious disease (ID) specialists and bedside discussion with doctors.

Currently, ciprofloxacin (except IV to oral conversion) is not one of the routinely monitored antibiotics under ASP in HA hospitals in Hong Kong. Extension of the scope of antimicrobial agents for ASP may be considered. Conducting DUE for ciprofloxacin to increase appropriateness of use is desired as literatures have already demonstrated positive results.

ANTIBIOTIC STEWARDSHIP PROGRAMME (ASP) in HONG KONG

ASP has been implemented in Hong Kong for over a decade. The following measures have been supported by literature to be useful as part of an ASP, and they also provide potential directions as a framework for future development of ASP.

1. Education and Guideline Development
2. Surveillance
3. Prescription Approval and Formulary Restriction
4. Information Technology Development and Support
5. Multidisciplinary Collaboration

1. Education and Guideline Development

Education is important to equip medical practitioners with adequate knowledge in antibiotic prescription, which is one of the more frequently prescribed drug classes. Studies revealed that 50-75% of emergency department or hospitalized patients received antimicrobials.[37] Significant deficiencies were seen in prescribing antimicrobial and upper-level residents were shown to be not more knowledgeable than the 1st-year residents about the antimicrobial use.[37,38] The role of education is thus a cornerstone to provide the fundamental knowledge for implementation of other ASP strategies[38-40] and influence prescribing behavior.[40]

Education can be in a variety of forms, from individual consultation to forum, lecture, newsletter, poster or mass email.[39,41] However, there is insufficient evidence to support that the use of one education measure over another is being the more effective.[38,39,41] due to the difficulties in assessing the outcome of different education programme.[38]

Table 1. Previous Antibiotic Stewardship Programme (ASP) and Drug Use Evaluation (DUE) studies in Ciprofloxacin or Quinolones

No.	Author, Place of study, Antimicrobial agent	Intervention	Study outcomes (Selected)
1	Hammerman *et al.*, Israel[36] IV and oral ciprofloxacin	Drug use evaluation, with education, intervention	Unjustified use had decreased from 31% to 13% (p<0.005)
2	Chang *et al.*, Taiwan[57] Parenteral agents	Prescription review and approval	Reduction of 4.2% in parental prescribed cases Total reduction in parenteral antibiotic usage (DDD/100 patient-days) was 13.2% Significant increases in the susceptibilities of *P. aeruginosa* to both amikacin and ciprofloxacin, and *Serratia* spp. to ciprofloxacin (p<0.05) Similar mortality, re-admission rates, and LOS
3	You *et al.*, Hong Kong[58] Meropenem, imipenem	Clinical guideline, seminars, prior prescription review	Prescription appropriateness increased significantly from 53.0% to 82%
4	Buising *et al.*, Australia[59] 3rd and 4th generation cephalosporins, carbapenems, glycopeptides, aminoglycosides, quinolones and extended-spectrum penicillins	Computerized antimicrobial approval system	Reduced trend of consumption in glycopeptides, carbapenems, aminoglycosides, quinolones and 3rd and 4th generation cephalosporins; with expected increase in consumption of extended-spectrum penicillins Similar 30-day mortality rate and LOS Increasing trend of susceptibility: *S. aureus* to methicillin, *Pseudomonas* spp. to carbepenems and aminoglycosides
5	Ng *et al.*, Hong Kong[60] Antipseudomonal cephalosporins, carbapenems, piperacillin-tazobactam, IV quinolones, IV marcolides, fluconazole	Guideline development, consumption monitoring, antimicrobial susceptibility pattern reporting, education and feedbacks	Significant reduction of restricted antibiotics (median monthly DDD/100 patients treated: -47.2%; median monthly DDD/1000 patient-days: -43.6%.) Significant reduction in mean LOS
6	Cheng *et al.*, Hong Kong[48] Broad spectrum IV antibiotics (piperacillin-tazobactam, cefoperozone-sulbactam, ceftazidime, cefepime, imipenem, meropenem)	Guideline development, 2-stage immediate concurrent feedback (Memo ICF and physician ICF)	Antimicrobial use decreased from 73.06 to 64.01 per 1,000 patient bed-day-occupancy Similar in crude mortality rate Reduction of piperacillin-tazobactam and ceftazidime-non-susceptible *K. pneumoniae*
7	Teo *et al.*, Singapore[49] Cefepime, ciprofloxacin, ertapenem, imipenem, meropenem, piperacillin-tazobactam	Two-stage prospective audit, IV to PO conversion, new guideline development	Significant reduction in the levels of consumption for total audited antibiotics (*p*=0.032), reduction is also seen in ciprofloxacin, piperacillin-tazobactam, imipenem No change for overall all-cause mortality rate and median LOS
8	Chan *et al.*, Taiwan[61] 30 parenteral agents	Computerized antimicrobial approval system (HCAAS)	Significant decrease in consumption: 3rd and 4th generation cephalosporins, fluoroquinolones and glycopeptides Similar inpatient mortality rate with a decreasing trend Isolation rate of MRSA started to decrease before HCAAS and continue later; Increasing isolation of extended-spectrum β-lactamase-producing *E. coli* and *K. pneumoniae*
9	Liew *et al.*, Singapore[32] Cefepime, ciprofloxacin, ertapenem, imipenem, meropenem, piperacillin-tazobactam, ceftriaxone, augmentin	Pre- and post-prescription review with feedback, guideline development	Significant increasing trend for total audited antibiotic consumption (p<0.05) largely contributed by meropenem and piperacillin-tazobactam; Significant decreasing consumption trend for IV ciprofloxacin and cefepime (p<0.05) Shorter average LOS (mean ± standard deviation 19.4 ± 19.9 days vs. 24.2 ± 24.2 days) No change for all-cause mortality (p=0.191) Significant lower infection-related re-admissions and 14-day re-infection rate
10	Niwa *et al.*, Japan[62] IV antibiotics in hospital (penicillins, 1st to 4th generation cephalosporins, carbapenems, Anti-MRSA agents, quinolones, aminoglycosides, others)	Pre- and post-prescription review with feedback, education, individual consultation	Significant reduction in consumption: 2nd generation cephalosporins (p=0.03), carbapenems (p=0.003), aminoglycosides (p<0.001) Reduction in the cost of antibiotics by 11.7% Mean LOS shortened by 2.9 days Significant reduction in appearance of MRSA from 47.6% to 39.5% (p=0.026); Proportion of *Serratia marcescens* to Gram-negative bacteria decreased significantly from 3.7% to 2.0% (p=0.026) Prolonged use of antibiotics over 2 weeks was significantly reduced (5.2% to 2.9%, p<0.001)

* DDD denotes defined daily doses, LOS denotes length of stay in hospital

Frequent review of antimicrobial guidelines is vital in providing the most updated therapeutic strategies for the clinicians. Guidelines development and regular review must involve collaborative efforts from ID specialists, clinical pharmacists with ID training, microbiologists, epidemiologists and infection control officers, etc.[29] When local guidelines are being developed, local practice in Hong Kong must be taken into account due to variance in resistance pattern, availability issue, etc.[41,42] The Hong Kong IMPACT Guideline has been used as guidance on local antibiotic utilization and the current 4th edition was published in 2012.

2. Surveillance

Close surveillance of antibiotic consumption and resistance data should be performed on a regular basis, which should include the annual preparation of antibiotic susceptibility data to various bacteria strains, also known as antibiogram.[29,40] By late 2000s, Singapore had a relatively high bacterial resistance rate which was believed to be contributed by a lack of emphasis of a systematic surveillance system.[43] Antibiogram must be produced at a local hospital level, taking into account local resistance data. Such data can aid in the development of antibiotic usage guidelines as well as provide important information for both a local and national surveillance programme. Ideally, antibiotic susceptibility data should be produced according to specialties. For example, resistant pathogens are identified more frequently in ICU rather than in general wards.[29,40] Meanwhile, analyzing the consumption data of antibiotics could explain the trend for the use and assist in devising strategies for optimization. Similarly, collecting consumption data according to different specialties and wards would be preferred. However this alone may not always reveal the appropriateness of use.[42]

Currently, surveillance programme is performed by National Healthcare Safety Network under CDC in the US and European Surveillance of Antimicrobial Consumption Network (ESAC-Net) in Europe.[43] Centre for Health Protection of the Hong Kong Department of Health publishes monthly antimicrobial data in out-patient setting while in-patient data are released internally by Hospital Authority.

3. Prescription Approval and Formulary Restriction

Prescription approval system is probably the single most effective intervention to optimize use of antimicrobials.[38,39] The process can be divided into pre- and post-prescription review. Indications, spectrum coverage, dosing and duration of the antimicrobial agent are considered in the pre-prescription approval process. Initial approval can be set in various forms, including the use of written and electronic antibiotic order form, verbal approval as well as face to face intervention assisted by clinical pharmacists on the ward, etc.[39,42] Post-prescription review is conducted 24-48 hours after the antibiotic has been given, usually when the microbiology data become available, and patients' clinical response to the initial treatment can be taken into consideration during this process.[29,41] Guideline suggests the narrowest possible spectrum antibiotic should be selected once culture report is ready.[44,45] However, many publications have revealed the tendency of physicians continuing with the initial agent, especially when improvement in symptoms or signs was observed.[46,47] Early intervention and re-assessment should thus be done 2-4 days after initiation of empiric treatment.[46]

A 2-stage immediate concurrent feedback (ICF) model was investigated by Cheng et al. in Queen Mary Hospital, Hong Kong, from 2004-2007.[48] In the first stage, ASP team reviewed and audited the selected broad-spectrum antibiotic prescription based on patient data and clinical information. Complicated cases or cases that were difficult to judge were referred to bedside consultation by ID specialists. As a result, antibiotic consumption reduced from 73.06 (baseline, year 2004) to 64.01 (year 2007) per 1,000 patient bed-day-occupancy.[48] Reduction of use and cost was observed in another similar study in Singapore. Improvement in clinical outcome, shorter length of hospital stay and reduction in re-infection within 14 days were noted.[32,49]

Formulary restriction is another strategy that is frequently implemented with prescription audit. After considering factors such as efficacy, safety profile, cost and local resistance pattern, different antimicrobials are included in the hospital's formulary. It is a decision made by the Drug and Therapeutic Committee of the hospital management (i.e. Drug Formulary Committee in Hospital Authority).

4. Information Technology Development and Support

The development of Information Technology (IT) application is closely linked to the successful implementation of surveillance programme and prescription approval system in ASP. A well designed computer surveillance system, such as the one that has been developed by CDC, can collect antibiotic use data and generate useful information for analysis, such as monthly use of a particular antibiotic, change of use pattern, demographics of patients by regimen, etc.[42] Tracking of resistance pattern is another advantage of the surveillance system.[40]

Computer-aided programme has great value in the prescription approval process. Clinical protocol or institution's guideline could also be incorporated into the computer system for decision making. The most well-known example was the system developed by Latter Day Saints (LDS) Hospital in Salt Lake City, USA.[50,51] The system supported auditing of antimicrobial prescription based on patient's medical record (any drug interactions, renal and hepatic function, etc.) and clinical condition. Significant reductions were seen in reported allergy, excess medical dosage, antibiotic-susceptibility mismatch, total hospital cost and length of stay.[40]

ASP written form is currently being employed in Hospital Authority for selected broad-spectrum antibiotics. Adopting electronic ordering review system may be the next step of ASP. IT personnel and management support are essential in designing and implementing a successful computer decision making programme that is compatible to the current system.

5. Multidisciplinary Collaboration

ASP is an interdisciplinary programme requiring expertise advice and input from healthcare professionals from different specialties and this important collaboration has also been emphasized in the consensus statement for ASP implementation in Hong Kong.[3] ID specialists, taking a leading role in the ASP team, are responsible in the review and update of institution's antimicrobial guidelines, the management of the antimicrobial formulary and providing training to other hospital staff.[40,52] Other members of the ASP team include clinical pharmacists, microbiologists, hospital epidemiologists, nurses and infection control officers. Clinical pharmacists with ID training can assist in formulary and guideline development, conduct DUE of antibiotic prescription to ensure compliance to guidelines and identify potential barriers to guideline implementation.[52] Support from microbiologists and hospital epidemiologists are vital as they are responsible for performing the surveillance work. Collaboration with nurses and infection control officers are also vital for infection control policy implementation on the ward level. Furthermore, the important role of IT experts in developing and ensuring a smooth operation of the computer programme cannot be overstated. Last but not least, strong support from hospital management is essential for the provision of the required manpower and access to the necessary hardware and software for the successful implementation of ASP.[3,40,43]

POTENTIAL BARRIERS OF ANTIBIOTIC STEWARDSHIP PROGRAMME (ASP)

Despite numerous benefits demonstrated in clinical studies, potential barriers of implementing ASP must be also considered. Acceptance and support of ASP by hospital staff from various departments can be one of the barriers. Physicians may have the feeling that their professional autonomy is threatened, especially for some specialists, as the daily clinical practice is intervened.[3,53] Early involvement of specialists in ASP may be a solution, for example, consulting their opinions while the guideline is being developed.[53] It is also important to change their mindset of considering individual's clinical outcome rather than resistance issue when prescribing antibiotics.[41]

Lack of human resources may be another barrier in implementing ASP. Clinical pharmacists trained in infectious disease were extremely rare in Europe.[54] There were only around 40 pharmacists specializing in infectious disease in US.[55] Incentives can be given from hospital management for pharmacists to receive training in infectious disease and participate in certified programme. Training programme in infectious disease requires 2 years of postgraduate work (residency and/or fellowship) in US.[56]

Implementing ASP demands a large increase in manpower and resources and thus requires additional financial support or redirection of resources for the institution. Hence, support from management is essential.[55] As discussed, the multidisciplinary team collaboration is also very important. Integration and co-operation work from microbiology laboratory, medical, nursing, infection control, pharmacy is challenging and this is another area that requires senior management's coordination.[3] Other potential barriers are the lack of specialized knowledge in infectious disease and IT support which have been discussed previously.

CONCLUSION

An increasing trend of resistance was observed in *P. aeruginosa* in surveillance studies and this may be associated with the increasing consumption of ciprofloxacin. Reducing usage of ciprofloxacin has been proven in studies to lead to a reduction of resistance in *P. aeruginosa* and thus preserve its superior orally active property against *P. aeruginosa*. This could be achieved by implementing ASP and DUE locally. Many DUEs have demonstrated increase in appropriateness of antibiotic prescription upon successful implementation of ASP. Meanwhile, the focus of ASP should be on education and guideline development, usage surveillance, prescription approval, formulary restriction and IT system development. Appropriate allocation of manpower and necessary resources by hospital management are also vital in promoting multidisciplinary collaboration. Consumption, expenditure and resistance problems are directly related to the curtail use of antimicrobials, but the therapeutic outcome would not be compromised according to literatures. Benefits are not only seen in ciprofloxacin but can be extended to other antimicrobial agents with a view to solving local resistance problem.

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Current and Alternative Uses of Oral Vitamin D in the Pediatric Population

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ABSTRACT

Oral vitamin D supplementation in the pediatric population is primarily indicated to prevent or correct inadequate levels resulting from conditions contributing to low vitamin D serum levels. These include chronic kidney disease patients, patients with intestinal malabsorption and those with drug induced hypovitaminosis. With these patients, pharmacists contribute towards optimizing drug therapy by recognizing such risk factors and ensure patients are provided with adequate supplementation. In recent years, several studies have reported additional benefits of vitamin D beyond its role in bone health. This has led to renewed interest in the use of vitamin D as clinicians explore the potential benefits beyond its current scope of use. By reviewing the current clinical recommendations alongside other potential benefits of vitamin D, pharmacists may better identify patients at risk for vitamin D deficiency, recommend sufficient supplementation corresponding with their vitamin D levels and understand the role of vitamin D in other novel indications.

Keywords: *Vitamin D, Oral Supplementation, Bone health, Infants, Children*

INTRODUCTION

Vitamin D supplementation in the pediatric population has been gaining attention in recent years. The increase in awareness is due to the recognition of factors that lead to sub-optimal bone health as a result of deficiency as well as emerging research suggesting potentially new therapeutic benefits of vitamin D.

Multiple factors contribute to vitamin D deficiency—patient's underlying condition, environmental factors as well as certain medications. Despite the long standing use of vitamin D in the pediatric population, a consensus on its clinical use remains inconclusive. In addition, a growing number of studies have suggested benefits of vitamin D extending beyond its musculoskeletal effects such as improved immune system modulation, endocrine regulation, and cardiovascular health.[1]

The objective of this article is to answer some frequently asked questions regarding the use of vitamin D in the outpatient pediatric population: (1) Who are at risk for vitamin D deficiency? (2) What are the current practice recommendations for the use of vitamin D in general pediatric population and in those with pre-disposing risk factors? (3) What are some of the newer evidence suggesting additional benefits of vitamin D supplementation?

VITAMIN D AND ITS ROLE IN PHYSIOLOGICAL PROCESSES

Vitamin D is an important hormone responsible for regulating certain mineral metabolisms. Though commonly named as a vitamin, it is in fact a steroid responsible for promoting phosphate and magnesium metabolism as well as stimulating calcium absorption in the intestine. Vitamin D is a fat soluble vitamin obtained from the diet in two forms: Vitamin D_2 and Vitamin D_3. Vitamin D_2, primarily found in fish and plants, is referred to as ergocalciferol. Vitamin D_3 on the other hand is formed predominantly after exposure to UV light and is referred to as cholecalciferol. Both forms are biologically inactive and collectively referred to as cholecalciferol or simply vitamin D.

Both forms of vitamin D are absorbed through our intestines, they are converted in the liver to the more stable form of calcidiol, known as 25-hydroxy-vitamin D. calcidiol circulates through our body by bounding to a protein known as vitamin D Binding Protein (DBP) and is eventually hydroxylated in the kidneys and other issues to the more potent form of vitamin D- Calcitriol, known as 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). Conversion of calcidiol to calcitriol largely occurs in response to low calcium, low phosphate or low parathyroid hormone levels. Calcitriol is 100 times more potent than calcidiol and is responsible for stimulating calcium and phosphate absorption from the small intestine, promoting secretion of calcium from bone into the blood, as well as phosphate reabsorption in the renal tubules. In a deficient vitamin D state, absorption of dietary calcium falls to 10-15% of intake and that of phosphorus falls to 60%.[2] The **Figure** depicts the pathway of vitamin D as it enters our circulation and its subsequent effects on the body. **Table 1** lists the definition of different terminologies related to vitamin D.

RISK FACTORS FOR VITAMIN D DEFICIENCY

Being out of the spot light for some time, vitamin D deficiency has recently re-emerged to become an important health problem especially among the pediatric population.[3-5] Skyscrapers, heavy pollution, widespread use of sunscreen

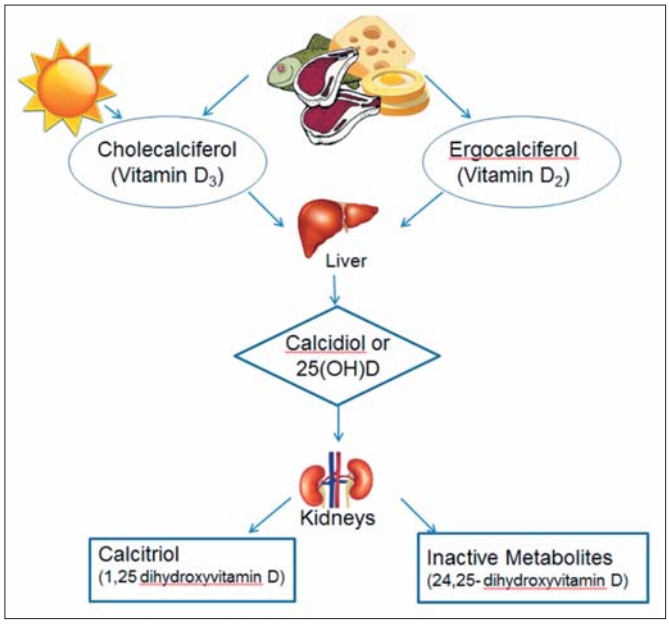

Figure. *Pathway for Vitamin D*

Table 1. Comparative Definition of Vitamin D Terminologies[1]

Common Name	Synonym	Description
Ergocalciferol	Vitamin D_2	Exogenous form of vitamin D; found usually in fish and plants. Biologically inactive
Cholecalciferol	Vitamin D_3	Endogenous form of vitamin D; synthesized by the skin from exposure to sunlight or dietary ingestion. Biologically inactive.
Calciferol	Vitamin D_2 or Vitamin D_3	Vitamin D without a subscript is collectively used to describe eiher vitamin D_2 or D_3
Calcidiol	25-hydroxyvitamin D / [25-(OH)D]	Precursor to Calcitriol and a more stable form of vitamin D in the body; serum level is the biological marker for bone health; synthesized from calciferol and regulated by the liver
Calcitriol	1,25-dihydroxyvitamin D/ [1,25-$(OH)_2$D]	Biologically active form of vitamin D; synthesized from calcidiol and highly regulated in the kidneys
Vitamin D Analogs	-	Refers to vitamin D forms that do not require hydroxylation (i.e.calcitriol, parcalcitriol)

and long hours of indoor activities limited the exposure to natural sunlight, which is an important element to stimulate our innate ability to synthesize vitamin D. In addition, people nowadays have been more aware of some other factors predisposing patients to vitamin D deficiency. Examples of such factors include medications (drug induced hypovitaminosis), deficiency secondary to a medical condition, or inadequate supplementation during pregnancy or breastfeeding.[6,7] Suboptimal levels of vitamin D among pediatric patients are of particular significance due to its impact on musculoskeletal growth. With approximately 90% of bone mass formed during childhood development, inadequate vitamin D levels may lead to fractures, rickets, osteoporosis and some conditions having poor prognostic outcomes. **Table 2** lists the causes for some of the risk factors as well as examples of conditions leading to vitamin D deficiency.

Clinical Recommendations

Serum level of calcidiol (25-hydroxy vitamin D) is the clinical biomarker used for monitoring an individual's vitamin D

Table 2. Risk factors for Vitamin D deficiency[6]

Causes	Examples
Reduced synthesis in the skin	Use of sunscreen; darker complexions; skin grafts
Decreased Absorption/ Bioavailability	Malabsorption and related diseases (e.g. Cysticfibrosis, Crohn's Disease, Inflammatory Bowel Disease, gastric bypass) Medications causing decreased fat intake (e.g. cholesterol sequestrates, orlistat) Obesity
Increased catabolism	Anticonvulsants, glucocorticoids, antiretrovirals, immunosuppressants
Inadequate supplementation	Inadequate maternal supplementation of Vitamin D and Calcium before and after pregnancy (during breastfeeding)
Reduced synthesis of 25(OH)D	Hepatic failure (vitamin D synthesis stops completely among patients with >90% hepatic dysfunction)
Increased urine loss of 25(OH)D	Nephrotic syndrome
Reduced synthesis of 1,25-$(OH)_2$D	CKD (some variations within the stages)
Acquired disorders[7]	Tumor-induced osteomalacia; Primary hyperparathyroidism; granulomatous disorders

status.[8,9] Although universal screening of vitamin D levels is not currently recommended due to low cost-benefit ratio, medical authorities do recommend screening for vitamin D deficiency in patients with risk factors.[2,8,10] Currently, there is no consensus on the ideal serum 25(OH) D level that correlates with good physiological bone health homeostasis. In their 2008 report, the American Academy of Pediatrics (AAP) set forth the recommendation of 400 IU daily vitamin D intake to achieve a target serum 25(OH) D level of >20 ng/mL.[10] This is similar to the Institute of Medicine (IOM) recommendation.[2,8] Both institutions indicate serum levels >20 ng/ml to be sufficient to support physiological functions although some inter-individual variations exist allowing some clinicians to target higher serum levels. European guidelines however, recommend slightly higher serum levels targeting above 30ng/mL. It should be noted that no therapeutic benefit has been reported with serum levels greater than 30ng/mL and doses around 1000 IU are usually needed to achieve such high target levels. Serum levels > 60 ng/mL have been strongly linked to negative outcomes and adverse effects while serum levels ≥ 150 ng/mL have been correlated with intoxication.[2] **Table 3** gives information on degrees of deficiency and its associated health outcomes.

Table 3. Serum 25(OH)D levels and associated health outcomes[2,11]

	Institute of Medicine		Endocrine Society		
Status	ng/ml*	nmol/L	ng/ml*	nmol/L	Associated Health Outcomes
Deficiency	<12	<30	<20	<50	Clearly associated with vitamin D deficiency, rickets in infants & children
Inadequacy/ Insufficiency	12 to <20	30 to <50	21-29	52.5 to 72.5	Consider inadequate, may pose negative effects on bone health or overall health
Sufficiency	20-50	50 to 125	30-100	75-250	Normal adequate level
Excess	>50	>125			May pose toxicity, potential negative outcomes

The recommended daily allowance (RDA) represents the daily intake sufficient for normal bone health, calcium regulation and metabolism in a healthy person. This value varies within the

pediatric population. Patients with minor forms of risk factors are encouraged to increase sun exposure to a reasonable amount as well as to increase intake of vitamin D rich food such as fish, cod liver oil or dairy food. Such recommendations may be sufficient as long as the patient is not presenting with symptoms of vitamin D deficiency such as generalized aches and muscle weakness, difficulty walking and standing, and other non-specific symptoms including irritability, lethargy, and developmental delay.[2,12]

However some patients may need direct supplementation, yet there is not sufficient evidence to recommend one form of supplement over another in general, with the exception that vitamin D analogs are recommended to be used in patients with kidney failure or hypoparathyroidism who have impaired 1-alpha-hydroxylation.[13] Vitamin D supplements can be taken with or without food. Although studies have reported an improved absorption of vitamin D_3 when accompanied by a high fat content meal, specifically those rich in monounsaturated fatty acids, this effect may not always lead to an increased serum 25(OH)D level.[14,15] **Table 4** summarizes the recommendations set forth by the IOM with regards to calcium and vitamin D supplementation. These recommendations are similar to that of the Endocrine Society.

Table 4. Institute of Medicine Recommendations: Dietary reference intakes for Calcium and vitamin D[11]

	Calcium		Vitamin D	
Age (for both gender)	RDA* (mg/d)	UL^ (mg/d)	RDA* (IU/d)	UL^ (IU/d)
0-6 months old	200+	1000	400+	1000
6-12 months old	260+	1500	400+	1500
1-3 yrs old	700	2500	600	2500
4-8 yrs old	1000	2500	600	3000
9-13 yrs old	1300	3000	600	4000
14-18 yrs old	1300	3000	600	4000

* Recommended Daily Allowance (RDA) refers to the amount that meets the needs of >97.5% of population

^ Upper Limit (UL) is the reference level of which intake above this level would result the risk of adverse events (1IU = 25ng)

\+ The value is Adequate intake (AI) which is by observed or experimentally determined approximations only

ROLE OF VITAMIN D IN CURRENT PRACTICE

Chronic Kidney Disease

Between 40-70% of children with chronic kidney disease (CKD) developed vitamin D deficiency leading to mineral and bone disorder (MBD) and resulting in a condition referred to as CKD-MBD.[16,17] This disorder is characterized by at least one of the following features: (1) Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; (2) Abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and (3) vascular or other soft-tissue calcification (extra-skeletal calcification).[18] This occurs due to the inability of the impaired kidneys to excrete phosphorus leading to hyperphosphatemia. Elevated serum phosphorus levels in turn reduce serum calcium and increase PTH levels causing utilization of calcium from the bone and subsequently poor bone health. The decline in serum calcium and vitamin D levels begins in the early stages of CKD and eventually there will be a cessation of 1,25-dihydroxy vitamin D production from the kidneys during renal failure.[19] CKD-MBD in the pediatric population becomes even more alarming as bone and mineral metabolism disturbances delay bone growth, induce deformities and affect the ability of the child's skeletal system to support future height and growth. The KDIGO guideline recommends monitoring of serum calcium, phosphorus and parathyroid hormone (PTH) as the primary markers to guide therapy in the treatment of CKD-MBD.[18] Vitamin D analogs may be used to manage PTH levels although comparison is difficult at this time due to insufficient data. Currently, guidelines recommend supplementation should be initiated when the serum 25(OH)-D level is below 30 ng/mL among CKD patients with Stage 2 to 4. **Table 5** summarizes the recommendations set forth by the KDIGO guideline. Active vitamin D analogs should be considered if serum PTH levels fall below the target range of 200 to 300 pg/mL despite the use of vitamin D formulations.[18]

Table 5. KDIGO Recommendations: Vitamin D deficiency treatment in pediatric CKD-MBD patient (Stage 2-4)[18]

25(OH)-D level (ng/ml)	Recommended Regimen
16 to 30	2000 IU/day OR 50,000 IU/month for three months
5 to 15	4000 IU/day OR 50,000IU every other week for three months
<5	8000 IU/day for four weeks, then 4000 IU/day for two months (total 3 months) OR 50,000 IU/week for four weeks, then 50,000 IU every other week (total 3 months)

High oral dose such as 600,000 IU has also been shown to be safe and effective in a prospective study among children with CKD stages 2 to 4.[17] Recently studies have suggested bone and mineral metabolism within this population to be directly correlated with cardiovascular health, with low vitamin D levels associated with an increased incidence of cardiovascular calcification and mortality.[17, 18] Adequate supplementation of vitamin D provides benefits both for bone and cardiovascular health.[20,21]

Bone Disorders

Chronic low bone mineral density due to vitamin D deficiency results in a condition known as rickets. Clinically, the condition may present as a delay in gross motor development, bone pain, widening of the wrists and ankles, delayed closure of fontanelles etc.[22] Although rather uncommon due to the fortification of some commercially available milk formulations and adequate nutrition among the pediatric population in Hong Kong, reports of local pediatric rickets have emerged in recent years. Current recommendations for management of rickets focus on correcting the underlying vitamin D deficiency.

X-linked hypophosphatemia (XLH)

X-linked hypophosphatemia (XLH) rickets occurs due to the mutation in the phosphate-regulating gene resulting in a homology to endopeptidases on the X chromosome (PHEX). Presentations of X-linked hypophosphatemia include phosphate wasting, hyperparathyroidism, bone deformities and short stature. Vitamin D_3 along with phosphate salts supplementation is the cornerstone of therapy used to reverse hypophosphatemia. Current recommendations suggest the use of calcitriol at an initial dose of 20 to 30 ng/kg/day in 2 to 3 divided doses along with elemental phosphorus 20 to 40 mg/kg/day in 3 to 5 divided doses.[23]

Malabsorption

Cystic fibrosis (CF) is a complex hereditary disease involving abnormal production of thick and viscous mucus in the lungs and digestive system. The Cystic Fibrosis Foundation Patient Registry Annual Report 2012 states that up to 14.8% of CF patients reported bone diseases such as fracture, osteopenia or osteoporosis.[24] Fat-soluble vitamin deficiency, including vitamin D deficiency is common among children with CF, likely attributed to the excessive mucus in the digestive system and CF-related pancreatic insufficiency leading to impaired absorption.[25,26] The Cystic Fibrosis Foundation recommends an initial supplementation of vitamin D_3 of 400–500 IU/day for children aged 12 months and younger, 800–1000 IU/day for 1–10 years of age and 800–2000 IU/day for 11 years and older targeting 25(OH)D level ≥30ng/mL after supplementation. Higher dose of vitamin D may be prescribed according to the guideline if serum levels do not reach target level.[27]

Patients with inflammatory bowel disease (IBD) may also be at risk for vitamin D deficiency due to the long-standing inflammation in the gut mucosa leading to impaired vitamin absorption. Chronic gastric inflammation also discourages children from adequate oral intake indirectly leading to induced anorexia and lactose intolerance.[28-30] The risk of developing skeletal complications is thought to be due to two mechanisms.[30,31] The first mechanism is the disease's effects on malnutrition and malabsorption of vitamin D and calcium. Although the role of inflammation and inflammatory mediators on calcium regulation is not well studied, current hypothesis suggests inflammatory mediators are able to induce changes in expression and activity of key Ca^{2+} transport proteins in the gut and kidney leading to impaired calcium absorption.[31] The second mechanism is thought to be due to the inflammation itself, accompanied by inflammatory mediators such as TNF, IL-1β and IL-6, affecting bone metabolism.

The Endocrine Society suggests a higher dose, either 2 to 3 times higher or in the range of 6,000 to 10,000 IU per day when treating vitamin D deficiency in patients with malabsorption syndromes.[2] This recommendation is not specific for the pediatric population and therefore should be used to serve as a reference to increase in doses rather than as a specific recommendation. Although a dose increase is recommended, some studies have reported a potential concern with the use of vitamin D in these patients. Considering the effect of vitamin D and calcium supplementation on BMD in these patients, studies reported rather insignificant benefits[29,32] with some suggesting a negative correlation.[33] One study reported a negative correlation between $1,25(OH)_2D$ and lumbar Z score (r=-0.31, p=0.005) in a subset of Crohn's Disease (CD) patients.[33] Although vitamin D is hypothesized to be beneficial for IBD management through immunomodulatory actions,[29,31] this is not supported by trials.[34]

Drug Induced Hypovitaminosis

Some medications pose a risk for vitamin D inadequacy or deficiency among pediatric patients. A number of which are well known examples such as antiepileptic drugs (AED), glucocorticoids, antifungals, antiretroviral medications and immunosuppressants. Mechanisms for such interactions are diverse but are primarily thought to involve pregame X receptors and cytochrome P 450 enzymes. Pregane X receptors (PXR) are members of the nuclear receptor superfamily and are involved in detoxifying xenobiotics and drugs. Activation of PXR leads to upregulation of 24-hydoxylase expression, the metabolic enzymes responsible for oxidizing calcidiol and calcitriol to their inactive metabolites (CYP3A4 is an example of 24-hydroxylases).[2,35] Other medications known to affect bone metabolism include antiretroviral therapy (ART). ART has been identified as a risk factor for vitamin D deficiency due to the ability of these medications to increase catabolism of $1,25(OH)_2D$.[2,6]

Antiepileptic drugs (AED) have been long associated with reduced bone mineral density and vitamin D levels.[36-38] AED-induced bone disease is influenced by the type, dosage and duration of antiepileptic therapy and has been detected in up to 50% of patients undergoing long-term antiepileptic treatment. Risk of bone disease is greater among patients taking CYP-inducers such as carbamazepine, phenobarbital, phenytoin and primidone. These AEDs activate PXR and consequently promote the breakdown of calcidiol and calcitriol as mentioned. However, AED-induced bone disease is also observed with the use of newer AEDs such as oxcarbazepine, valproic acid, gabapentin, lamotrigine and levetiracetam which have little or no enzyme inducing effect suggesting other probable mechanisms of the interaction between AEDs and vitamin D.[35]

Osteoporosis due to glucocorticoids is a significant risk factor for pediatric patients on long term therapy. Several mechanisms account for glucocorticoid- induced osteoporosis and increased risk for fractures: 1) glucocorticoids increase osteoclast activity 2) glucocorticoids decrease production of sex hormones thereby reducing the latter's protective effects on the bone and 3) glucocorticoids inhibit intestinal calcium absorption while increasing renal calcium excretion both of which may result in hypocalcemia. Some glucocorticoids (such as dexamethasone) also activate pregane X receptors leading to degradation of 25 (OH)D and $1,25\ (OH)_2D$.[35]

Currently, the National Endocrine Society suggests children on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole and medications for AIDS be given vitamin D supplementation 2 to 3 times higher than the recommendations corresponding to their age group (at least 6,000-10,000 IU/day) to correct vitamin D deficiency, followed by maintenance therapy of at least 3,000-6,000 IU/day.[2] A 2015 review article suggests a minimum of twice the RDA of vitamin D_3 supplementation be considered when treating children with rheumatic conditions particularly patients on glucocorticoids. The recommendation proposed a dose of 1500-2000 IU/day for infants 6-12 months old; 2000 IU/day for children1-8 years old; 2000 IU/day for boys aged 9-18 years; and 2000-3000 IU/day for girls aged 9-18 years.[39]

POTENTIAL NEW ROLES FOR VITAMIN D

Although the role of vitamin D has largely been correlated with bone health, studies have suggested potential benefits extending beyond that of the skeletal system. Recent studies suggesting an alternative benefit of vitamin D will be presented below. It is to note the use of vitamin D for such indications in clinical practice is still in its infancy.

Autoimmune Effects

Vitamin D in its active form -1,25$(OH)_2$D- has recently been recognized for its immune-modulatory and anti-inflammatory properties. Studies reporting the prevalence of a vitamin D deficient state among patients with immune and auto-immune related conditions such as asthma, allergic rhinitis, atopic dermatitis, rheumatic disease, systemic lupus erythematous (SLE), etc, independent of the other risk factors, have correlated its potential benefit apart from that in bone health.[40-42] This correlation suggests the possibility of an underlying vitamin D deficiency independent of glucocorticoids use - a mainstay treatment option in many of these conditions. Low vitamin D levels, as determined by serum levels of 25(OH)D < 20 ng/mL, was in fact found to be common among patients with SLE and had been associated with elevated SLE disease activity index (SLEDAI) scores.[43] A cross-sectional study looking at the effects of supplementation with 2,000 IU/day of vitamin D_3 and 600mg calcium twice daily in 28 Saudi children with SLE reported 17 of the 28 subjects showed improvement in SLE disease activity score and autoantibody profile despite most subjects already on an 800 IU/day vitamin D_3 supplement prior to enrollment. The study further showed the effects eventually plateaued after 3 months of supplementation suggesting reaching homeostasis range. Toxicity might occur with high doses therefore further increase in doses was not recommended.[44] Other studies have also found vitamin D deficiency as a potential risk factor to develop avascular necrosis (AVN) - a known complication of SLE. Compared to subjects with no prior incident of AVN, vitamin D deficiency is more prevalent in AVN subjects (52.9% vs 28.3%; p=0.034).[43]

Children with atopic dermatitis (AD) may also benefit from vitamin D supplementation. A recent cross-sectional analysis among 39 children with AD showed a 3-month vitamin D supplementation of 1,000 IU/day significantly reduced AD severity and altered cytokines levels from baseline.[45] Supplementation of 1,000 IU/day of vitamin D_3 for one month during the winter had also shown to result in significant improvement in AD severity scores among 104 children with winter-related AD.[46]

Studies have previously suggested the benefit of vitamin D in reducing the number of asthma exacerbations.[47,48] A 6-month randomized, double-blind study among 48 children with newly diagnosed asthma was conducted to examine the effects of inhaled steroid (budesonide 800µg/day) with or without vitamin D_3 at 500 IU/day. The study reported the percentage of children with exacerbations to be significantly lower in the steroid with vitamin D_3 arm (17% vs 46%; P=0.029).[49] A similar double-blind placebo-controlled randomized study (n=100 asthmatic children) showed similar findings with a significant reduction (0 exacerbations in 72% vs 40%; 1 exacerbations in 18% vs 34%; 2 exacerbations in 6% vs 8%; P<0.01) in the number of exacerbations among children receiving oral vitamin D_3 60,000 IU every month for 6 months.[50]

Central nervous system (CNS) Effects

Patients with seizures are at risk for severe injuries such as falls and fractures; a risk further worsened by poor bone health.[51] Insufficient vitamin D levels had been previously reported to be prevalent among children with epilepsy. Vitamin D levels were also found to be significantly higher in those without the condition (18.5ng/mL vs 15.3ng/mL, p=0.004).[36] Children with epilepsy had also been reported to have reduced bone mineral density (BMD) when compared to control,[52] however this finding was not substantiated in other studies.[36] In patients with refractory conditions, use of multiple agents may be necessary, this is a recognized predictor of low BMD in children as many AEDs may cause reduction in serum 25 (OH) D levels.[36] Patients with refractory seizures may try ketogenic diet, this is a factor that has also been associated with declining vitamin D levels despite the increase in serum concentrations shortly after initiation of the diet.[53]

A study investigating the use of vitamin D supplementation among children and adolescents (n=78) age 10 to 18 years of age on long-term AED therapy reported serum 25(OH) D levels to have increased significantly from baseline after 1 year of receiving vitamin D 400 IU/day (18.2ng/mL to 21.3ng/mL, p=0.012) or 2000 IU/day(18.0ng/mL to 22.9ng/mL, p=0.001). After 1 year of supplementation, 50% of children were considered to have sufficient levels while 44% had inadequate levels and 6% of all children remained vitamin D deficient. This might indicate the need for higher supplementation among certain patients such as those with progressively increasing high doses of AEDs. The authors concluded that children receiving vitamin D supplementation either 400 IU/day or 2000 IU/day showed an increase in BMD with levels remaining elevated throughout the duration of the study.[54]

Cerebral palsy is a motor impairment disorder resulting from an insult that occurred sometime during the developmental process. It is often accompanied by a non-progressive neurological deficit with clinical presentations ranging from mild motor disturbances to severe total body involvement.[55] Adequate vitamin D and calcium supplementation in these patients is crucial as patients with cerebral palsy are at risk of osteopenia and even osteoporosis, due to immobility, low intake of minerals and abnormal vitamin D metabolism especially among those treated with anticonvulsants.[56] An open-label, non-randomized controlled trial showed 0.25 µg/day of calcitriol and 500mg/day calcium supplementation in a group of severely disabled children with CP in full-term care (n=23) greatly increased BMD during the 9-month period (0.383 g/cm^2 to 0.476 g/cm^2, p<0.001).[56]

Low levels of vitamin D have shown to correlate with poor quality of sleep, poor performance and daytime sleepiness. The hypothesized mechanism of which is thought to be due to the inhibition of tumor necrosis factor-α (TNF-α), interleukin-1(IL-1) and prostaglandin D_2 (PD_2) production, all of which are sleep regulating substances.[57-61] Low vitamin D levels have also been associated with non-specific pain and non-inflammatory skeletal myopathy, which potentially impair sleep and consequently daytime activity impairment.[61]

Infectious Diseases

Antiretroviral therapy (ART) has been identified as a risk factor for vitamin D deficiency due to the ability of these medications to increase catabolism of 1,25$(OH)_2$ D.[6] However additional benefits of vitamin D supplementation have been reported as well. Vitamin D deficiency in HIV-infected patients has been associated with a higher viral load and greater immune suppression.[62] A randomized placebo-controlled trial conducted in 50 children and young adults with HIV reported

the benefits of 7000 IU/day of vitamin D_3 given for 12 months. The study showed vitamin D at the given dose significantly increased naive T helper cells % (P<0.01), significantly reduced viral load (P<0.05) and marginally increased CD4% (P<0.1).[63] A prospective randomized 12-week study examined the effects 7,000 IU/day vitamin D_3 supplementation in 59 children and adults with HIV, significant increases in CD4% and reduction in viral load (P<0.04) were observed.[64] Both studies indicated the beneficial effects of vitamin D in promoting antibacterial immunity among HIV-infected patients with no adverse effects reported.[63,64] The HIV virus has been found to impair bone integrity through impaired bone calcium utilization and reduced osteoblast activity.

Studies have also reported the role of vitamin D supplementation in the prevention and management of respiratory infections. The benefit stems from the observation of an inverse relationship between vitamin D levels and incidence rate among patients with influenza, pneumonia and other respiratory infections.[65] A randomized, double-blind trial conducted among 244 Mongolian children with vitamin D deficiency reported significantly fewer acute respiratory infections during the winter in the group receiving milk fortified with 300 IU of vitamin D_3 compared with the group receiving normal milk (P=0.047).[66] A second randomized, double-blind, placebo-controlled trial in Japan conducted among 167 school aged children showed significant reduction (RR: 0.58; P=0.04) in the incidence of influenza A in the winter among those receiving 1200 IU/day of vitamin D_3 supplementation.[67] The effect was much more prominent in children who were vitamin D supplement naive (RR: 0.36; P=0.006).[67]

However studies conducted had failed to identify the association of vitamin D supplementation with reduction in incidence of pneumonia. Studies had reported no difference in incidence (0.145 per child per year vs 0.137 per child per year, incidence ratio: 1.06; 95%CI: 0.89-1.27), duration to recovery (72 hours vs 64 hours, p=0.33) and resolution of symptoms in pneumonia in the pediatric population.[68-70]

Endocrine Effects

Several studies have acknowledged the role of vitamin D in the prevention and treatment of patients with diabetic mellitus. Low vitamin D levels have been identified as a potential risk factor for developing Type 1 diabetes due to specific receptors in pancreatic β cells that work more effectively in vitamin D sufficient states. The various endocrine effects of vitamin D may be explained by the presence of vitamin D receptors in pancreatic β cells, adipocyte and muscle cells. Some of the proposed beneficial effects of vitamin D may occur via upregulation of the expression of insulin receptors and glucose transporters, regulation of calcium levels, modulation of immune and inflammatory cytokine expression by direct effects on pancreatic β-cell function and insulin secretion.[71,72]

An open-label, non-randomized controlled study reported vitamin D levels to be inversely correlated with $HbA1_C$ (r=−0.30, p=0.01) and insulin resistance (r=−0.31, p=0.03) among type 2 diabetic patients (n=79).[72] The study also showed vitamin D levels to be positively correlated with glutathione (GSH) levels (r=0.26, p=0.05), which protected against the increased oxidative insults common in diabetic patients.[72] A cross-sectional study conducted among postmenarchal female adolescents (n=47) demonstrated total 25-hydroxy vitamin D to be strongly associated with high vitamin D binding protein (r=0.57, p<0.0001). Vitamin D binding protein is the carrier protein specific for vitamin D. High levels of this protein was found to be positively associated with whole body insulin sensitivity (r=0.33, p=0.002), inversely associated with fasting insulin level(r=-0.51, p=0.0003) and homeostatic basal insulin resistance (r=-0.45, p=0.0002).[73] This effect is similar to that between insulin resistance and other well-known hormone binding proteins such as sex hormone-binding globulin.[73,74]

Cardiovascular Effects

Recent studies have demonstrated an association between vitamin D deficiency and cardiovascular diseases through multiple mechanisms, including suppression of renin-angiotensin-aldosterone system, anti-inflammatory action and down regulation of PTH.[75,76] A double-blind placebo controlled study conducted among 80 infants with congestive heart failure showed beneficial effects of vitamin D. The vitamin D group received supplementation of 1,000 IU/day of vitamin D_3 oral drops, after 12 weeks, a significant improvement in HF score, left ventricular (LV) end-diastolic and end-systolic diameter, LV ejection fraction were observed in the vitamin D group compared to placebo group (P<0.001).[77] Other studies have identified hypocalcemia as a rare but reversible cause of dilated cardiomyopathy in infants[78,79] Supplementation of vitamin D and calcium has been shown to be beneficial,[78,79] although at this point it is difficult to provide any concrete recommendations from the existing evidence. Uncertainty lies whether the deficiency itself is associated with the severity of cardiovascular diseases, or vitamin D supplementation contributes to improved clinical outcomes.[75,76] Although current evidence remains inconclusive, these studies suggest infants with CHF may benefit from vitamin D supplementation in accordance to the IOM guideline or at a higher dose as adjunctive treatment in heart failure to improve cardiovascular outcome.

Hematology and Oncology Effects

Vitamin D deficiency in patients with thalassemia has been linked to bone diseases and cardiac dysfunction despite adequate exposure to sunlight and routine supplementation of 400-1,000 IU of daily vitamin D.[80] However, evidence to support such use remains inconclusive. The 2013 guideline published by The International Network on Growth Disorders and Endocrine Complications in Thalassemia (I-CET) lists vitamin D supplementation as a Grade C recommendation.[81]

In patients with hemophilia, vitamin D supplementation may provide some benefit. A recent review on bone health among patients with hemophilia indicated the relatively high prevalence of low bone mineral density (BMD). The authors concluded that such prevalence of low BMD should warrant active screening and treatment of vitamin D deficiency in both children and adults with hemophilia.[82] A descriptive study on 47 children with severe hemophilia in Turkey had also identified high prevalence of vitamin D deficiency and advised routine checking of vitamin D levels twice a year along with vitamin D supplementation to ensure sufficiency.[83]

Vitamin D has been shown to be beneficial in the management of some cancers such as breast cancer, prostate

cancer and colorectal cancer with recent studies showing vitamin D to possess antitumor activities hypothesized to be due to actions against sustained proliferative signaling, tumor-promoting inflammation, resistance to apoptosis, angiogenesis, etc.[84,85] Additional beneficial roles include inhibiting cell proliferation, inducing apoptosis/differentiation, inhibiting angiogenesis/metastasis and inhibiting inflammation.[86] There have also been studies reporting benefits in the recovery of survivors with studies showing low serum 25 (OH) D levels to be common among survivors of childhood cancer which may impact the recovery of bone mass after chemotherapy.[87,88] Reasons for such low levels may be due to insufficient sun exposure and/or dietary intake. Although there are no concrete recommendation currently regarding the amount of vitamin D supplementation for cancer patients, a reasonable approach would be to administer 800IU/day vitamin D_3 as used in a randomized, double-blind, placebo-controlled trial (n=92).[89]

Metabolic Syndrome

Metabolic syndrome (MetS) is a cluster of multiple cardiometabolic risk factors and is an underlying cause of most chronic diseases, including type 2 diabetes, cardiovascular disease (CVD), stroke and kidney failure. Its own development is related to insulin resistance, a condition promoted with vitamin D deficiency.[90] A triple-masked controlled trial involving adolescents with MetS (n=50) looked into the use of 50,000 IU vitamin D_3 weekly for 6 weeks. The study supported the use of vitamin D concluding the favorable effects of supplementation on reducing insulin resistance and improving cardiometabolic risk factors in obese children.[91] In addition, significant reductions in serum insulin (p=0.04; p=0.02) and triglyceride concentrations (p=0.04; p=0.02) were also found, when compared with baseline and with control group.

Vitamin D may also be critical in lipid profile management. In a meta-analysis conducted, higher serum 25(OH) D was reported to relate to more favorable lipid profile in the pediatric age group.[92] A weak association between serum 25(OH) D and triglyceride levels was also reported (r=-0.135, CI: -0.243, -0.025), but the association was less significant to that of total cholesterol (r=-0.086, CI: -0.0205, 0.035) and LDL-C (r=-0.025, CI; -0.22, 0.17). The authors concluded that the association between 25(OH) D and HDL-C was direct and significant (r=0.156, CI; -0.021, 0.324). **Table 6** summarizes the recommended doses of vitamin D for different indications.

CONCLUSION

Vitamin D supplementation among the pediatric generation has been a long-standing clinical treatment for vitamin D deficiency secondary to various conditions and even medications. Newer applications of vitamin D as suggested by the article offer potentially new therapeutic areas for vitamin D outside its musculoskeletal benefits. Although some require further validation due to conflicting results--such as pneumonia, hepatic disorders and inflammatory bowel disease--clinicians may consider using vitamin D supplementation while adhering to the recommendations by the Institute of Medicine. In most of the cases maintaining adequate vitamin D level by daily supplementation as per IOM recommendation is a reasonable option. Further studies are needed to determine vitamin D's role in the aforementioned new indications in order to provide solid evidence-based recommendations on the new uses of vitamin D.

Author's background
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Table 6. Comparative Recommended Doses of Vitamin D based on Indication

	Indication	Suggested Dose	
Current Practice Recommendations			
Renal Impairment[18]	Chronic Kidney Disease Bone Mineral Disorder (CKD-BMD)	Refer to Table 5	
Bone Disorders[2,22]	Rickets	Initial Treatment: 50,000 IU of vitamin D_3 once a week ≥ 6 weeks Maintenance: 0-12months old: 400-1000 IU/day Children: 600-1000 IU/day	
Drug Induced	AEDs, glucocorticoids, antifungals (i.e. ketoconazole), antiretroviral agents	Initial Treatment: 2 to 3 times above the recommendations corresponding to their age group (at least 6,000-10,000 IU/day) Maintenance: 3000 - 6000 IU/day	
Possible New Therapeutic Areas			
Immunological	Rheumatic diseases[41]	6-12 months: 1500-2000 IU/day 9-18 years old (boys): 2000 IU/day	1-8 years old: 2000 IU/day 9-18 years old (girls): 2000-3000 IU/day
	Atopic Dermatitis[45,46]	1000 IU/day during winter	
	Asthma	Children: 600 IU/day	
Central Nervous System	Bone problem related to epilepsy, cerebral palsy	0-12 months: 400 IU/day	Children: 600 IU/day
	Sleeping disorders	0-12 months: 400 IU/day	Children: 600 IU/day
Cardiovascular System	Heart failure[77]	1000 IU/day	
Endocrine System	Diabetes Mellitus	0-12 months: 400 IU/day	Children: 600 IU/day
Infections	HIV infection[62,63]	Initial Treatment: 6,000-10,000 IU/day to correct deficiency Maintenance: 3,000-6,000 IU/day HIV Disease Control: 7,000 IU/day	
	Influenza prophylaxis	0-12 months: 400 IU/day	Children: 600IU/day
Hematology & Oncology	Thalassemia Major[81]	Maintenance: 800-1,000 IU/day	
	Hemophilia	0-12 months: 400 IU/day	Children: 600IU/day
	Oncology[89]	800IU/day vitamin D_3	

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Current and Alternative Uses of Oral Vitamin D in the Pediatric Population

1. Which of the following patients are at risk of Vitamin D deficiency?

(i) A 8-year-old boy with his epilepsy well-controlled by both levetiracetam 40mg/kg/day and carbamazepine 10mg/kg/day, and has been using them for 1 year.

(ii) A 1-year-old girl who has been using topical 1% hydrocortisone for her eczema for 1 week.

(iii) A 12-year-old obese boy who play indoor computer game all the day and refuse going outdoor.

A. (i) and (ii) only
B. (i) and (iii) only
C. (ii) and (iii) only
D. All of the above

2 CE comes to your community pharmacy with her 6 year-old boy. She claimed that her child to be a "picky eater" and is therefore nutritional deficit. The boy has not been on any medication. CE ask for your recommendation for a multivitamin product. As per the IOM's recommendations, which of the follow daily Vitamin D content will you be looking for?

A. 400 IU
B. 600 IU
C. 800 IU
D. 1000 IU

3. As per the KDIGO guidelines, which of the following is true regarding to managing children with chronic kidney disease with mineral and bone disorder (CKD-MBD)?

A. Only patients with a 25(OH)D level below 15 ng/mL requires supplementation with Vitamin D.
B. For stage 2 to 4 patients with a 25(OH)D level 5 to 15 ng/mL, ergocalciferol 4000IU every other week for three months is recommended.
C. High doses as much as 600,000 IU orally hav been shown to be unsafe and ineffective and are not recommended.
D. Monitoring parameters include serum calcium, phosphorus and PTH levels.

4. In which of the following conditions have there been studies reporting insignificant benefits or even a negative impact of Vitamin D supplementation?

A. Inflammatory Bowel Disease
B. Asthma
C. HIV infection
D. Hemophilia

5. The following drugs are known to pose a risk for Vitamin D inadequacy or deficiency, except:

A. Glucocorticoids
B. Antacids
C. Antifungals
D. Antiretroviral medications

6. Which of the following conditions demonstrate benefits of Vitamin D supplement?

(i) Poor bone health associated with epilepsy and cerebral palsy
(ii) Sleeping Disorder
(iii) Heart failure

A. (i) only
B. (i) and (ii) only
C. (ii) and (iii) only
D. All of the above

7. Vitamin D is positively associated with the following, except:

A. Insulin sensitivity
B. Glutathione (GSH)
C. Vitamin D binding protein
D. None of the above

8 Which of the following is/are the consequence(s) of activation of the pregnane X receptor that oppose the actions of Vitamin D?

A. Upregulation of metabolic enzymes that degrades calcidiol and calcitriol
B. Inhibition of calcitriol conversion in the kidney
C. Activation of osteoclast
D. All of the above

9. Which of the following is/are the benefit(s) of Vitamin D supplementation in children with asthma?

A. Reduced use of inhaled steroid
B. Improving lung function reported as FEV1 (Forced expiratory volume in 1 second)
C. Reduced number of exacerbation
D. All of the above

10. Which of the following correctly describes the benefit(s) of Vitamin D supplementation shown in children regarding infectious diseases?

(i) Vitamin D supplementation during winter reduces the incidence of influenza.
(ii) Vitamin D supplementation speed up recovery of pneumonia.
(iii) High dose Vitamin D supplementation helps with HIV management by enhancing immune function and potentially reducing viral load.

A. (i) only
B. (i) and (ii) only
C. (i) and (iii) only
D. All of the above

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 233(D&T)

Considering Cognitive Function Treatment in Major Depressive Disorder

1. D 2. A 3. B 4. A 5. B 6. D 7. D 8. B 9. C 10. C

A Heuristic Study on the Effect of Zika Viral Transmission on Human Health

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ABSTRACT

Zika virus (ZIKV) is an infectious pathogen, which is a mosquito-borne flavivirus. It was first identified in monkeys then in humans in 1952. It is primarily transmitted by Aedes mosquitoes and other possible transmission means which are described in this review article. People with ZIKV disease show several symptoms like fever and skin rash. There are scientific data indicating that this infectious disease may associated with some serious illnesses in human, e.g. Guillain-Barre syndrome and microcephaly. Since there is no effective treatment or vaccine available to cure this viral disease, the safest way to avoid infection is to protect oneself against mosquito bites. This review summaries some scientific discoveries on what have been found relevant to this disease.

Keywords: *Zika virus, mosquito bites, infectious pathogen, fertility, fever, Guillain-Barre syndrome, microcephaly, vaccine*

INTRODUCTION

Zika virus, commonly abbreviated as ZIKV, is a recently discovered pathogen that we do not have too much knowledge about. Reports and studies regarding this pathogen was scarce until earlier this year when there was an outbreak in South America. On 1 February, 2016, the World Health Organization (WHO) declared public health emergency on International concern after a lot of cases of ZIKV infected people in Brazil. It was after this even that a boom of research about the Zika virus in order to understand and to learn how to control the spread of this virus.[1] The earliest report of this virus was its isolation from a sentinel Rhesus monkey in the Zika forest in Uganda in 1947. A year later, the virus was isolated from a species of mosquito, *Aedes africanus*, also in the same forest.

The first human infection was reported in 1953 in Nigeria.[1] The virus, however, is spread throughout Asia and Africa. Clinics in these regions are used to Dengue and Chikungunya fever which can be easily detected. But as the Zika virus is not as familiar as the others, it can be easily misdiagnosed.[2] Today what people know is its spread in three geographical distinct viral lineages but there is little known about their genetic relationship.[2] The two major lineages are the one including the African strain and the one with Asian and American strains. The East African cluster includes the one found in Eganda in 1947.[3]

STRUCTURE OF ZIKA VIRUS

Zika virus is a member of *Spondweni serocomplex* within the Flavivirus genus and Flaviviridae family which also includes Dengue fever.[2] Flaviviruses are small single-stranded positive RNA virus, with a length of 10794 nucleotides (ZIKV MR766).[3] A detailed cryo-EM mapping of the virus revealed that the surface of ZIKV is covered by some tightly-packed enveloped proteins and glycosylated amino acid as shown in **Figure 1**. **Figure 2** is a cross section of the viral particle during its transfection of a cell. It shows that the RNA genome with capsid proteins is surrounded by some membrane proteins embedded in the lipid membrane and the envelope protein, which is found on the outermost surface. The ZIKV infect the cell by binding to the carbohydrate receptors on the cell surface, then a single strand of the viral RNA is chaperoned by many capsid protein to process assembly and infection.

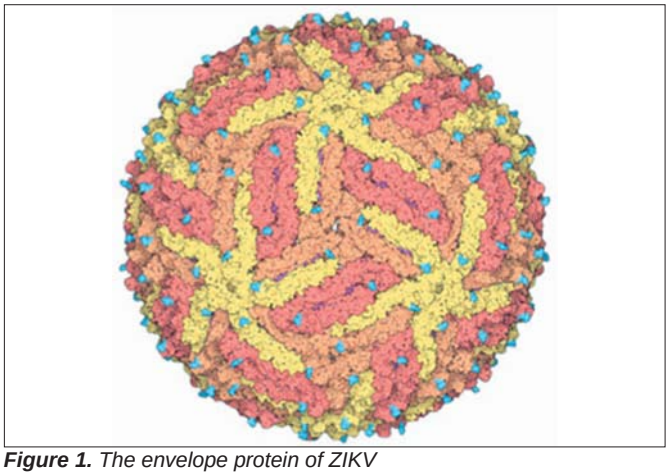

Figure 1. *The envelope protein of ZIKV*

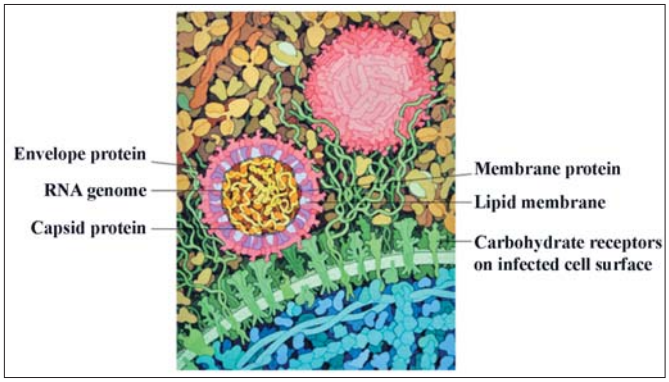

Figure 2. *Cross section of ZIKV during its transfection process.*

EPIDEMIOLOGY AND TRANSMISSION OF ZIKA VIRUS

There have been a few outbreaks of ZIKV, which are the main events for studying the virus and from where we have collected most knowledge from. The breakout in Yap Island in the Federated States of Micronesia, 2007 was the first reported epidemic. Seventy three percent of the population in the island was infected. The symptoms were mostly mild and not for a long time. The French Polynesia had a large breakout during October, 2013 to April 2014 where 66% of the population were infected. During this period, 42 cases of Guillain-Barré Syndrome was reported, which compared to 3 cases in 2012, raised a huge concern by scholar.[1]

The globally distribution of mosquito *Aedes aegypti* has been identified as a likely vector for ZIKV transmission. **Figure 3** shows the spread of ZIKV; of which we know of and the different locations of *A. aegypti* and *A. albopictus* mosquitos. By comparing diagram A and B of Figure 3, which is the location of outbreaks and evidence of Zika and the location of spread of the mosquitos, respectively, it is obvious that the locations overlap quite well. In some subtropical areas, where the spread of Aede mosquitos is common, ecological analyses would suggest a risk of ZIKV. But this conclusion could not be applied to Northern Australia or parts of North America because there is no sign of the virus. Are these areas at risk or not is hard to say since no similar virus has been identified. Unlike Dengue fever, which occurrence could be found in diagram C **(Figure 3)**, Zika virus is failed to spread there. Nevertheless, an outbreak in these area might be possible if a traveler spread through some limited ways such as sex and blood transfusion.[1]

Human skin cells are permissive for ZIKA infection and replication.[4] Hence, the main way of being infected is getting bitten by a mosquito carrying the virus. During the blood-feeding process of ZIKV-carried mosquitoes on human skin, the virus is inoculated and then localized to the epidermis and dermis of human skin. **Figure 4** shows the expression of RNA determined at different time points after human skin biopsy specimens is infected by ZIKV.

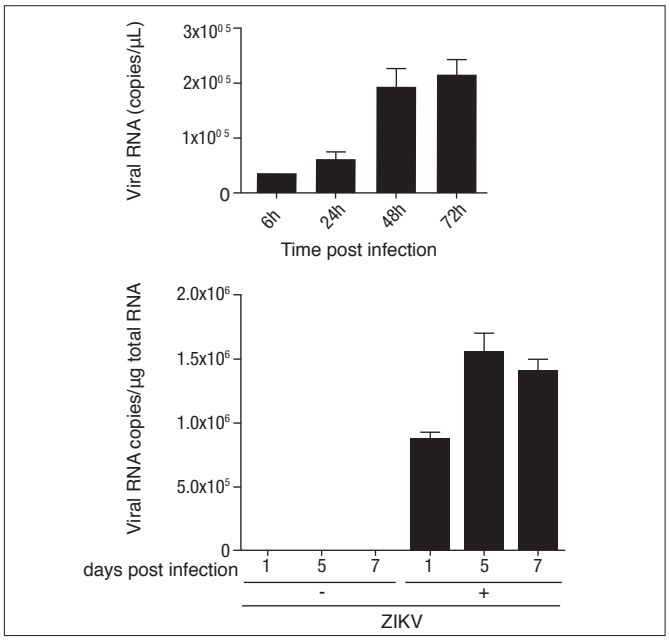

Figure 4. *Viral RNA expression when human skin biopsy specimens infected with ZIKV.*

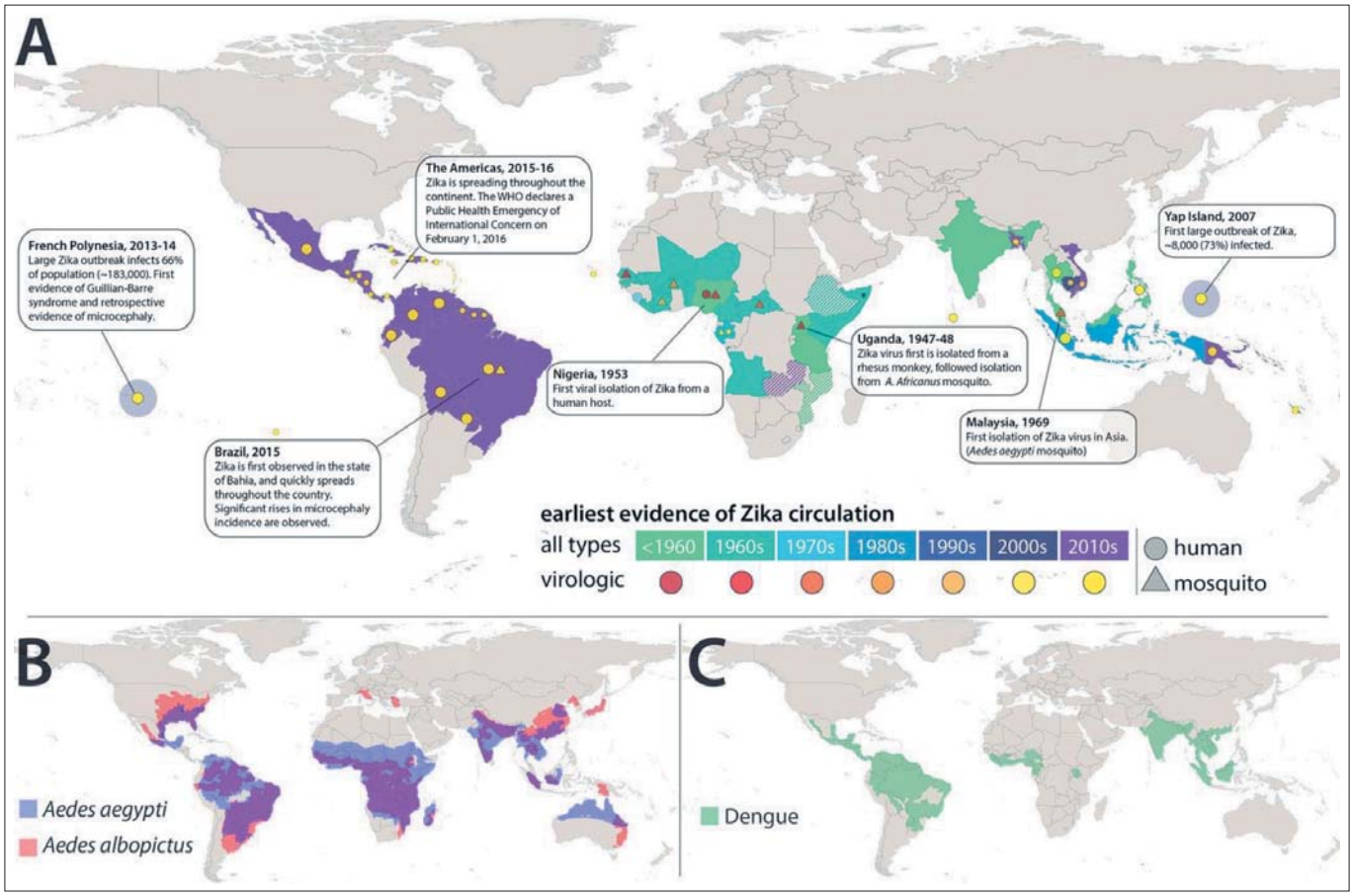

Figure 3. Reported outbreak and potential distribution of ZIKV. A: *Spread of ZIKV color coded by earliest evidence of ZIKV;* ***B:*** *Locations of ZIKV vectors Aedes aegyti and Aedes albopicturs;* ***C:*** *Map of presence of Dengue fever.*[1]

However, mosquito bite is not the only channel for human to get infection by the virus. Transmission and spread of ZIKV between human could also be accomplished by blood transfusion, congenital, perinatal or sexual transmission.[5,6]

SYMPTOMS AND HEALTH EFFECT

ZIKV could be highly-spread in short time because most of its infection is asymptomatic. The clinical features of ZIKV are mild and only last for a few days, some of them includes skin rash, fever, conjunctivitis (having red eyes), muscle or joint pain and general malaise.

1. General Health Effect

1.1 Acute disseminated encephalomyelitis and damage of brain cells

It is a Central Nervous System (CNS) disease which was recently found to be one of the possible neurologic manifestations risks under ZIKV infection.[7] What's more, the consequences of ZIKV infection towards human neuro-cells are being investigated by scientists. **Figure 5** shows the detailed infection process and situation of ZIKV to human neuro cell under experiment simulation setting, which concludes that ZIKV can induce cell death in human neural stem cells and thus causing brain function impairments.[8]

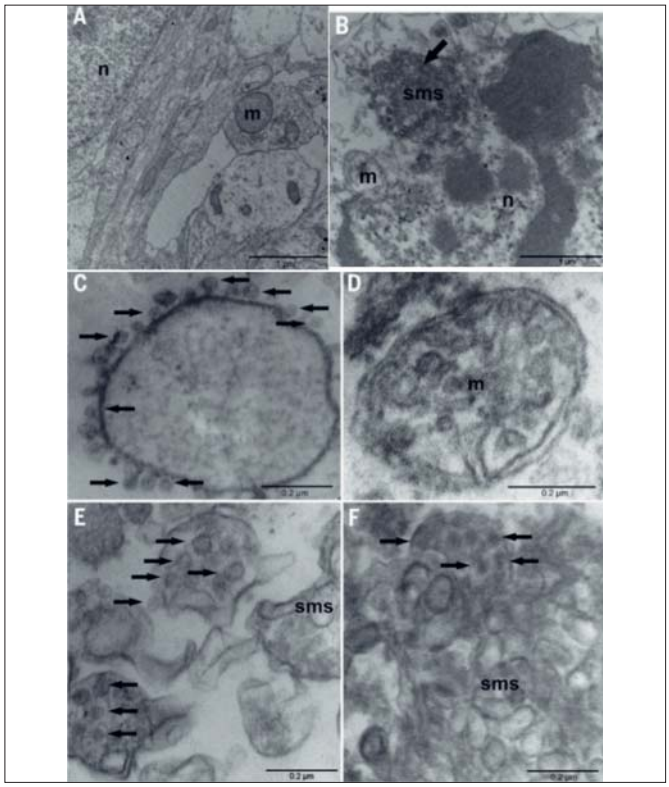

Figure 5. The ultrastructure of neurospheres after 6 days of in vitro infection by ZIKV.
(A) Mock-infected neurosphere showing cell processes and organelles.
(B) ZIKV-infected neurosphere showing a pyknotic nucleus, swollen mitochondria, smooth membrane structures, and viral envelopes (arrow).
(C) Viral envelopes on the cell surface (arrows).
(D) Swollen mitochondria.
(E) Viral envelopes inside the endoplasmic reticulum (arrows).
(F) Viral envelopes close to smooth membrane structures (arrows).
Scale bars, 1 μm in (A) and (B) and 0.2 μm in (C) to (F).
m, mitochondria; n, nucleus; sms, smooth membrane structures.

1.2 Guillain-Barre Syndrome (GBS)

It is an uncommon disease of nervous system. According to Science Magazine, some ZIKV patients develop an autoimmune response that attack their own nerve cells, leading to muscle weakness and paralysis. It was noted that the GBS is usually temporary - 80% of patients can walk unconditionally again after six months; while there are 5% of patients whose breathing ability will be affected by the GBS paralysis, which may lead to death.

2 Health Effect Regarding Pregnancy and Children

2.1 Microcephaly

ZIKV infection in pregnant women causes Microcephaly in their babies, which means the baby's head is smaller than the normal one (Shown in **Figure 6**).[9] ZIKV infects the brain cells, particular an important cell called Neural Progenitors which form critical grey matters in the brain. Once ZIKV enter these cells, virus replicate until the cell overwhelm and burst, which allow the virus further spread into the brain. What's more, the ZIKV also causes Calcifications (i.e. scars) in the brain that disrupt the connections between parts of the brain. Which finally leads to not enough pressure from the tissue within the skull to push the skull outward to form a normal shape head.

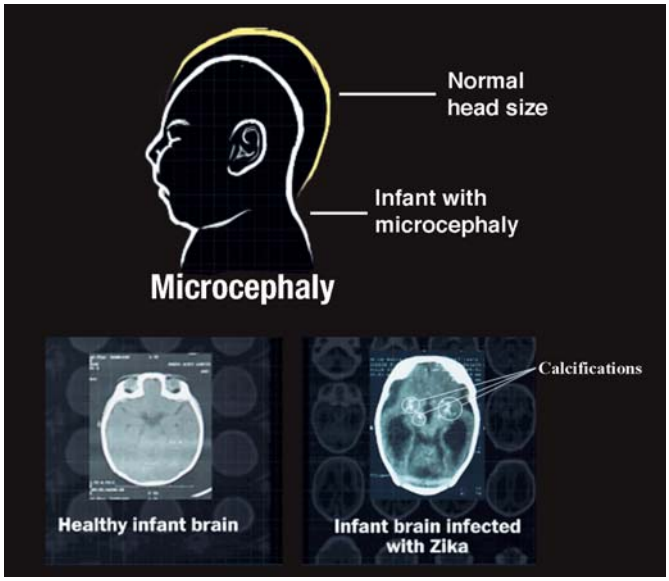

Figure 6. *The comparison of head and brain between normal infant and infant infected with ZIKV.[10]*

2.2 Congenital Zika Syndrome

There are some birth defects found on babies when the mother is infected by ZIKV during pregnancy.[10] For example damage to the back of the eyes, joints with limited range of movement like clubfoot and too much muscle tone that restrict body movement after birth.

3 ZIKV Impact on Men's Fertility

More recently, a study concerning the Zika virus impact on men's fertility has been reported.[11] The study was done on mice and reveals that the Zika virus could lead to worrisome consequences for men regarding their fertitlity. It has been previously known that ZIKV can persist for months in men's semen and infect others during intercourse. Three weeks after the mice were infected with the virus, their testicles shrunk to

one tenth of their original size, as shown in **Figure 7**. In addition, their levels of sex hormones were lower and their fertility was reduced. When mating with female mice they were four times less likely to impregnate them. Since the study was made on mice we cannot be sure that humans will suffer the same effect, but the researchers seem to believe it is very likely. Also, we don't know if the effect is permanent but it is most likely since the virus infect and destroy the Sertoli cells, which are the cells that hold the internal structure and they don't regenerate.[11]

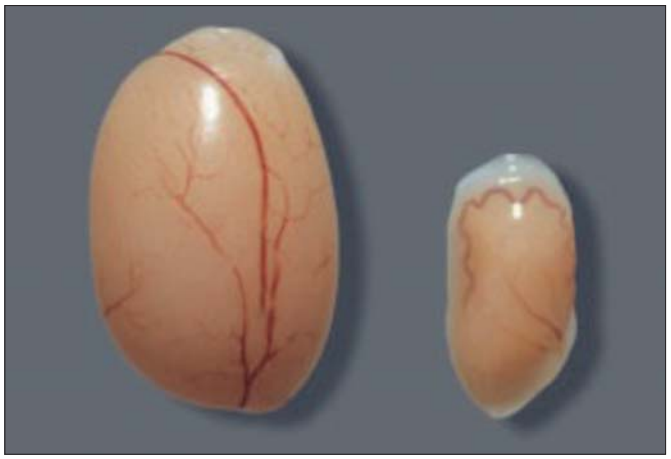

Figure 7. Mouse testicles before (left) and after (right) infected with ZIKV.[11] *The testicles of male mice showed cellular damage and shrinkage three weeks after Zika infection. On the left is a healthy mouse testicle; on the right, a testicle following Zika infection.*

PREVENTION AND CONTROL

The application of a ZIKV vaccine would be the best choice to prevent a population at risk. However, development of ZIKV vaccine is merely being pursued by the WHO and many governments. According to WHO statics, there are at least 18 active manufacturers and research institutions engaging in its early stages of vaccine development. None of them has been passed the phase I of clinical studies; i.e. an effective vaccine is still unavailable at this moment.

Since no specific therapy is available, treatment is symptomatic. Complete bed rest and good nursing care are probably the best approach. The patient should be kept under mosquito netting until the 2nd fever has abated in order to prevent transmission to mosquitoes. Fluids should be forced and an ice cap used to relieved headache. Severe headaches and bodily aching may be alleviated with paracetamol or aspirin.

Reducing ZIKV incidence via vector control or limit ZIKV exposure similar to the control of dengue fever may be an alternatively approach to control the transmission of ZIKV. Effective vectors had been used for successfully control or elimination of yellow fever in many countries during the 20th century although they have been proven unsustainably eliminating the disease. Nevertheless, adopting vector control has some short-term benefits.

CONCLUSION

After analyzing and consolidating information from various scientific studies and health organizations' reports, it is concluded that the viral RNA of ZIKV is surrounded by proteins, once the viral cell blind to the receptor of the human cell, the viral RNA enter, assembly and replicate and thus infect the patient. Other than the primary source of ZIKV (i.e. the Aedes mosquitoes), the virus can also be transmitted through mosquito bites, blood transfusion, sexual activities, or by congenital or perinatal transmission. The symptoms of ZIKV infection are mild and disappear quickly that people may not be able to realize. However, the health effect and possible risks are significant, such as damage of brain cells, Guillain-Barre Syndrome (GBS), microcephaly in babies if the mother is infected by ZIKV during pregnancy and probably infertility in man if testis is affected.

The long-term aspect concern from both public and physical points of view is that ZIKV may cause various problems to a society. The microcephaly causes stillbirth or death for children, which may deteriorate the population competitive of a society in the long run. On top of that, if the corpse of patient is not well treated and the living virus inside is transmitted again by insects, like mosquito and fly, the epidemic situation may further worsen, i.e. public health problem eventually. During the SARS outbreak in Hong Kong in 2003, statistic showed that the Hong Kong happiness index slumped significantly at that time. This indicates that an outbreak of epidemic diseases can significantly damage the social mental well-being, and so does ZIKV. In a nutshell, the infectious ZIKV causes many serious physical diseases, potential public-health issues and long-term health problems.

Author's background

Miss ALBÉRT Anna Maria *is an exchange student while* ***Mr. CHEUNG Tsz Yan*** *is a local student. Both were doing a general education course on Health & Lief given by Dr. CHEUNG in City University of Hong Kong during the semester A of year 2016-17.*

Dr. CHEUNG Hon Yeung*, who is an associate professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong since 1989, is a manufacturing pharmacist and biotechnologist. He has numerous publications and received many awards in both his research and academic career.*

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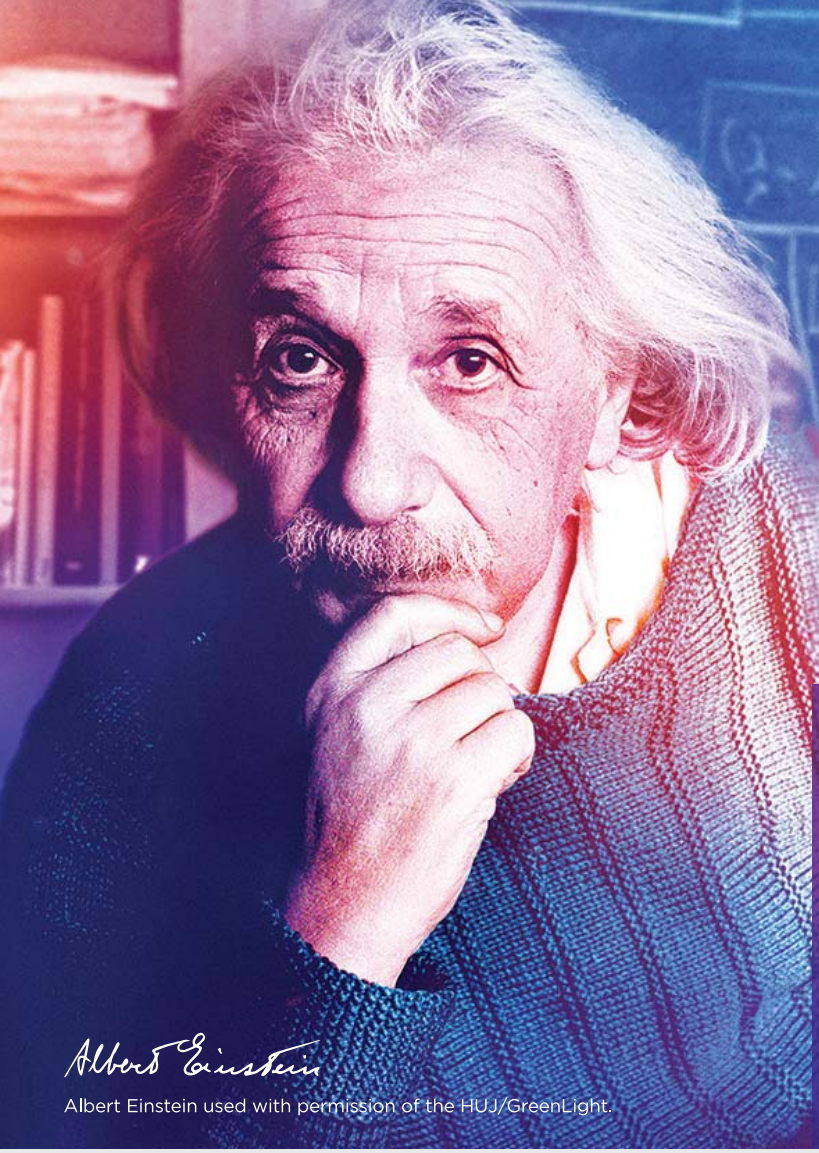

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  - Overall cure rates of 94–99% across phase 3 studies[1,3–6]

LOW DISCONTINUE RATE

- **99%** completed regimens of up to 12 weeks[7]
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- **ONE** pill, once a day[1,d]
  - Single-Tablet Regimen for the majority of HCV GT1 patients[1,d]

☑ IFN free ☑ RBV free[d] ☑ PI free

[a] As assessed by the Metavir fibrosis stage scoring system.

[b] HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. 99% cure rates were observed in the ION-1 study in previously untreated HCV GT1 patients treated with HARVONI for 12 weeks. Across the ION studies, SVR rates between 94–99% were observed in HCV GT1 patients treated with HARVONI for 8–24 weeks. 99% of patients completed regimens of up to 12 weeks.[1]

[c] Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment. Achieving SVR is considered a virologic cure.[2]

[d] HARVONI offers a single-tablet, ribavirin-free regimen for the majority of HCV GT1 patients, excluding those with decompensated cirrhosis, or who are pre- or post-liver transplant, etc.[1]

HARVONI®
ledipasvir/sofosbuvir

Harvoni® Abbreviated Prescribing Information

Presentation: Orange colored, diamond-shaped, film-coated tablet containing 90 mg ledipasvir and 400 mg sofosbuvir.
Indications: Treatment of chronic hepatitis C genotype 1 infection in adults.
Dosage: Adults: One tablet taken orally once daily with or without food. Pediatric Use: Safety and effectiveness have not been established. Geriatric Use: No dosage adjustment is warranted in geriatric patients. Renal impairment: No dosage adjustment is required for patients with mild or moderate renal impairment. Safety and efficacy have not been established in patients with severe renal impairment or end stage renal disease requiring hemodialysis. No dosage recommendation can be given for these patients. Hepatic impairment: No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment. Safety and efficacy have not been established in patients with decompensated cirrhosis. Pregnancy: Harvoni should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.
Warnings and Precautions: Serious symptomatic bradycardia when coadministered with amiodarone: coadministration of amiodarone is not recommended. Counseling patients about the risk of serious symptomatic bradycardia and cardiac monitoring are recommended for patients taking amiodarone, patients starting amiodarone therapy and patients discontinuing amiodarone just prior to starting Harvoni; Risk of reduced therapeutic effect due to P-gp inducers: use with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended; Related products not recommended: use with other products containing sofosbuvir is not recommended.
Adverse reactions: The most common adverse reactions were fatigue and headache in subjects treated with Harvoni during clinical trials. Serious symptomatic bradycardia has been reported in patients taking amiodarone from postmarketing experience.
Drug interaction: Any interactions that have been identified with ledipasvir and sofobuvir individually may occur with Harvoni. P-gp inducers (e.g., rifampin or St. John's wort); Acid reducing agents including antacids (e.g., aluminum and magnesium hydroxide), H_2-receptor antagonists (e.g., famotidine) and proton-pump inhibitors (e.g., omeprazole); Antiarrhythmics (amiodarone, digoxin); Anticonvulsants (carbamazepine, phenytoin, phenobarbital, oxcarbazepine); Antimycobacterials (rifabutin, rifampin, rifapentine); HIV antiretrovirals [combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate (TDF), regimens containing TDF and a HIV protease inhibitor/ritonavir (e.g., atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir), combination of elvitegravir, cobicistat, emtricitabine and TDF, and tipranavir/ritonavir]; HCV products (simeprevir); Herbal supplements (St. John's wort); HMG-CoA reductase inhibitors (rosuvastatin).
Before prescribing, please consult full prescribing information which is available upon request.
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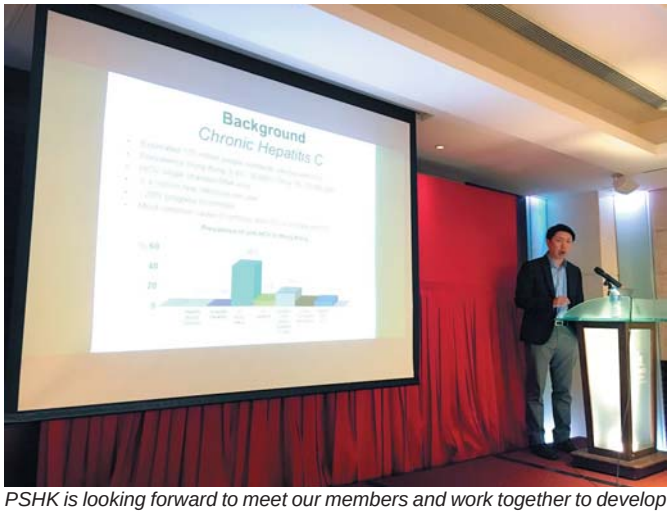
PSHK AGM and Annual Dinner 2016

The Pharmaceutical Society of Hong Kong (PSHK) held its Annual General Meeting (AGM) and Annual Dinner on 3 Dec 2016.

The new General Council (GC) members for 2017 were elected at the AGM. We are happy to have a good combination. Our GC members work in different sectors in pharmacy: hospital, community, industry, academia, etc. Besides, we have some experienced GC members but at the same time, we have some GC members who are newly registered pharmacists. We believe this good team mix can better contribute to the development of our pharmacy profession.

Another new initiative for PSHK this year is that we have created two new positions: Head of Public Education and Head of Professional Continuing Development. The reason to have these new positions is due to the increased focus and workload of PSHK on public education and pharmacist professional development. We hope we can improve our effort and resources in these two areas in order to better serve our member and the general public.

After AGM, Prof Ivan Hung from the University of Hong Kong delivered a lecture on updates on hepatitis C treatment. The lecture is very comprehensive on the past, present and future medications for hepatitis C and Prof Hung shared some of his clinical experience with our members.



PSHK is looking forward to meet our members and work together to develop our pharmacy profession.

PSHK General Council Members 2017

President	Mr. Philip CHIU			
Vice Presidents	Mrs. Mary CHENG	Mr. Edward YAU		
Hon. Secretary	Ms. Cadence YAN			
Hon. Treasurer	Ms. Tony LI			
General Committee members	Mr. CHENG Wai Chung	Mr. Chris LEE	Mr. Dick SUNG	Mr. Rico YAU
	Mr. Marco CHEUNG	Mr. Peter LEUNG	Ms. Eliza TAM	
Pharmacy & Poisons Board members	Ms. CHIANG Sau Chu	Mr. Benjamin KWONG	Mr. Andy WONG	
Head of Public Education	Mr. Matthew WONG			
Head of Professional Continuing Development	Dr. Keary ZHOU			

SHPHK 30th Anniversary – A time to reflect and look ahead

Reported by
YIU, Kenneth, MPharm, PgDip (Clin. Pharm), Executive Manager of the Society of Hosipital Pharmacists of Hong Kong.

In the coming year 2017, the Society of Hospital Pharmacists of Hong Kong (SHPHK) will celebrate its 30th anniversary and will take this wonderful opportunity to reflect, reminisce and take stock of where it all began. The Society was founded in 1987 and over the time has evolved from a small professional body with little social profile or market presence, to an established organisation attracting members from various sectors of the profession. The Society takes pride of its remarkable accomplishments, with many of which at the beginning supposedly unachievable, achieved over its past 30-year journey. On the last issue of the year, the Society would like to share with you some of the activities we organised in 2016, and on some forthcoming events in year 2017.

Young pharmacist's Forum

This year, there has been concern on employment prospects in pharmacy. In view of this, a Young Pharmacist Forum was hosted on 20th August, 2016 at the Chinese University of Hong Kong 伍何曼原樓, with an aim to let our participants voice out their concerns and, to share views on the future development of the profession. Many speakers were invited to offer our audience some advice on interview techniques and coping strategies to withstand the pressure during this challenging period. Over 120 participants attended the forum including local and overseas pharmacy students, as well as current pharmacist interns. The Society has received some positive feedbacks from many attendees who thought the forum was enlightening and some went into great length to contribute to the Society after this event.

The Young Pharmacists Forum aimed to open up dialogues across the floor and to help the audience to explore opportunities and career paths.

Education and training for members

SHPHK views continuing professional development (CPD) is an integral component in the continuing provision of safe and effective services for the benefit of our service users. In 2016, SHPHK delivered a series of educational seminars on topics including immunotherapy, PIVAS, precision medicines, and medication safety. The Society has the honour to have invited Professor Vivian Lee, Mr. Michael Ling and Ms. Amy Chu to deliver a seminar on biosimilar following their completion of a biosimilar course at the National Institute of Bioprocessing Research and Training (NIBRT) in Dublin. The Society was also very pleased to observe a high attendance rate in each teaching seminar, indicating that many members in the profession do embrace on the concept of CPD. As a persisted commitment to foster the continued professional education culture, SHPHK would continue to provide more educational seminars to member pharmacists in the coming year.

Biosimilar seminar: Ms Amy Chu delivered her presentation on the complexity in the production processes of biologics.

Hong Kong and Conde S. Januario Hospital (Macau) pharmacists Visiting and Experience Exchange Programme

On the 3rd December 2016, the Society hosted an exchange programme with a group of pharmacists from Macau to visit the North Lantau Hospital and Queen Mary Hospital. On arrival at the pharmacy in the North Lantau Hospital, participants were astonished by the purpose-built-dispensary design and the high level of automation that helped to stream-line the workflow and reduce the patient waiting time. At the second half of the programme, the group arrived at the Pharmacy Department of Queen Mary Hospital to view the aseptic manufacturing. This visit program not only enabled effective communication and exchanges between pharmacists of two regions, but also fostered professional collaboration through sharing experiences and good practices on hospital pharmacy management.

Public engagement and drug education

SHPHK continued to focus on engaging the public to promote safe and effective use of medication. In this respect, Drug Education Resources Centre (DERC), an affiliating organisation of SHPHK, submitted more than 40 educational articles to the local newspapers. For example, the Society recognised that antibiotic resistance is a growing issue that affect the globe. Hence in Mid November, the Society supported the World Antibiotic Week by publishing "「抗生素耐藥性」你要知！" on Headline Daily (頭條日報). The article was written in a Q and A format aiming to raise awareness on antibiotic resistance and to encourage best practices among the general public to avoid further emergence and spread of the resistance. DERC also had exposure on other mass media with Ms Daisy Lam, associate director of DERC, interviewed on various radio and television channels.

An educational advertorial for antibiotic resistance published on the Headline Daily on 14th November 2016

The launch of DERC website

In year 2017, DERC will be celebrating the official launch of its new public educational website. The DERC website is a patient empowerment platform that provides the public with an easy access to the medication information, with an aim to facilitate self-management and encourage discussions with their healthcare providers. To ensure the information on the site is credible, up-to-date and can be easily understood by the public, all content editorial work is managed by a team of member pharmacists dedicated on public education. Thanks to our 'responsive' website design, which enables user-friendly navigation through the website on multiple device platforms such as smart phones or tablet PC. DERC website will continue to enhance, as we shall see new features adding to DERC by phases, including our drug search engine which will soon be available to the public, allowing enquiry on over 20,000 registered pharmaceutical products in Hong Kong.

The launch of Drug Education Resources Centre (DERC) website is expected to be in the first quarter of 2017

All and all, year 2017 will truly be an exciting year for the pharmacy profession and public drug education. To celebrate its 30th Anniversary, the SHPHK will be organising a series of events throughout the year, all details of which to be announced in due course, hoping to engage all of our collaborating partners as represented by the four figures in the DERC logo that symbolises the relationship between patients, public, physicians and pharmacists who are caring for each other. SHPHK and DERC would continue to dedicate on the advancement of pharmacy profession, and strive to enhance public medication use through technology and education.

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Erratum

In the last issue of Hong Kong Pharmaceutical Journal Vol23 No 3, page 86, title "Review of Newly Registered Oncology Drugs in Hong Kong", the name of one of the author is spelled incorrectly. It should be "EWIG, Celeste Lom Ying" instead of "EWING, Celeste Lom Ying.

Dear Fellow Pharmacists,

As you all know, the Hong Kong Pharmacy Conference will be held on 18 and 19 February 2017 at the Hong Kong Convention & Exhibition Centre. Since it is the most important annual event for pharmacists in Hong Kong, the Organizing Committee, with representatives from seven co-organizers, namely the Chinese University of Hong Kong, the Department of Health, the Hospital Authority, the University of Hong Kong, the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong, has put a lot of efforts to design the program and to prepare for the Conference.

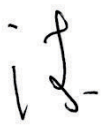
The theme of the coming Conference is "To Innovate and Excel". We aim at bringing the latest innovations and advancements in the field to inspire you. To highlight a few, we have invited Professor Dennis Lo to share his experience in his development of non-invasive prenatal testing, which benefit many mothers and babies; Professor Ronald Li will introduce his human heart-in-a-jar and its applications in drug discovery; Dr Mark Neuenschwander from the United States will share his knowledge and experience in merging IT technologies and medication; Professor Ram Mahato, also from the United States, will talk about recent advance in nucleic acid-based therapeutics.

Apart from the fully-packed academic programs, we will continue to have poster presentations, exhibition booths and a full-of-funs Conference Dinner. What's more, there will be lots of familiar faces and chances to make new friends.

This Conference is for YOU! So if you have not yet registered, please do so today!

See you all at the Pharmacy Conference!

Cheers,



Lot Chan
Chairman
Hong Kong Pharmacy Conference 2017

- Non-invasive Prenatal Testing: From Dream to Reality
- Pharmacist Clinic in Pain and Palliative Care – Clinical Sharing
- BEERS for Elderly: To START or To STOPP? How a Pharmacist should Review Medications for Elderly
- Recent Advance in Nucleic Acid-based Therapeutics
- Innovative Dispensing System: Hub and Spoke
- Molecular Testing in Diabetes – What, Why and How
- Integrating Data for Drug Utilization Evaluation in the Big Data Era

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2017 18-19 FEBRUARY
HK Convention & Exhibition Centre

www.pharmacyconference.org

KEYTRUDA (Pembrolizumab) Solution for Injection

By WONG Anna (Bachelor of Pharmacy, HKU 2016)
(Edited by LEUNG Lucilla)

Indications:
Keytruda is indicated for
- The treatment of patients with unresectable or metastatic melanoma
- The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA

Dosage and Administration:
Select patients for second line or greater treatment of metastatic NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression. The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Withhold KEYTRUDA for any of the following:
- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Grade 3 or 4 endocrinopathies
- Grade 2 nephritis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:
- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
- Grade 3 or 4 nephritis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions

Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line.

Note: This summary does not include all parts of the prescribing information due to limited space. Please refer to the full prescribing information for further details.

Forensic Classification:
P1S1S3

NEW INDICATION

PRADAXA®
(Boehringer Ingelheim)

Prepared and edited by CHAN Ivy

Active Ingredient:
Dabigatran etexilate

Presentation:
Each hard capsule contains 75 mg of dabigatran etexilate (as mesilate).
Each hard capsule contains 110 mg of dabigatran etexilate (as mesilate).
Each hard capsule contains 150 mg of dabigatran etexilate (as mesilate).

Pharmacological Properties:
Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.
Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin bound thrombin and thrombin induced platelet aggregation.

Indications:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors:, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Dosage & Administration:

Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery (pVTEp orthopaedic surgery)

Patients following elective knee replacement surgery

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1–4 hours of completed surgery with a single capsule of 110 mg and continuing with 2 capsules once daily thereafter for a total of 10 days.

Patients following elective hip replacement surgery

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1–4 hours of completed surgery with a single capsule of 110 mg and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For the following groups the recommended daily dose of Pradaxa is 150 mg taken once daily as 2 capsules of 75 mg.

Treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules once daily thereafter for a total of 10 days (knee replacement surgery) or 28-35 days (hip replacement surgery):

- Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min) [see Renal impairment *(pVTEp orthopaedic surgery)*]
- Patients who receive concomitant verapamil, amiodarone, quinidine [see Concomitant use of Pradaxa with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amidarone, quinidine or verapamil *(pVTEp orthopaedic surgery)*]
- Patients aged 75 or above [see Elderly *(pVTEp orthopaedic surgery)*]

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Prevention of stroke and systemic embolism (SEE) in adult patients with NVAF with one or more risk factors (SPAF)

The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)

The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding . Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

SPAF, DVT/PE

For the following groups the recommended daily dose of Pradaxa is 220 mg taken as one 110 mg capsule twice daily:

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups, the daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

For DVT/PE the recommendation for the use of Pradaxa 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

In case of intolerability to dabigatran, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options for prevention of stroke and SEE associated with atrial fibrillation or for DVT/PE.

Elderly (SPAF, DVT/PE)

Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). The renal function should also be assessed at least once a year in patients treated with Pradaxa or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc)

Patients at risk of bleeding (SPAF, DVT/PE)

Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test (see section 4.4) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastrointestinal bleeding).

See full monograph for full posology and administration

Forensic Classification:

P1S1S3

Toujeo®
insulin glargine 300U/mL

心臟安全認證*,1

減少低血糖風險[2]

新一代 長效胰島素

傳承優良，突破界限！

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一日一針[5]，24小時全日控糖

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- 更少出現低血糖†,[2]
- 更少體重上升[2]

*Toujeo®之成分的心血管安全性已獲歐盟EMA認證[1]
†EDITION 1, 2及3臨床測試之集合分析結果[2]

EMA：歐洲藥品管理局(European Medicines Agency)
圖片僅供參考，注射筆上之標籤並非香港批核認可之版本，請以產品實物為準。

參考資料：
1. European Medicines Agency. Toujeo : European Public Assessment Reports. 2015 May 07. 2. Clements JN, Bello L. Am J Health Syst Pharm 2016;73:359-66. 3. Data on file. 4. Becker RHA, et al. Diabetes care 2015;38:637-43. 5. Toujeo® European Medicines Agency Summary of Product Characteristics. 2015 Feb.

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