



NewsLetter

院訊

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- Bronchoscopic Lung Volume Reduction

Pharmaceutical Update



MESSAGE

FROM THE MEDICAL SUPERINTENDENT



Dr. William Ho
Medical Superintendent

120 Years of Achievements – What's Next?

By God's grace, St. Paul's Hospital has served the Hong Kong community well for 120 years, and growing from strength to strength. This time we dedicate a separate issue – in fact our 100th issue – of the SPH Newsletter to commemorate the event. Here I just like to express my deepest gratitude to the Congregation for their immense support in all the celebratory activities, all the VIP guests for their gracious presence and words of wisdom, all the staff members who worked tirelessly to make the events most impressive and memorable, and all doctors and other guests who took the time to participate and share our joy.

To tally, we organized a Celebration Mass, a Fun Run, a Relay Run, a Baby Crawling Competition, a Community Health Day, a History Corner, a Harp Performance, a Grand Opening Ceremony and a Celebration Dinner – all smoothly organized and superbly delivered. I could see the pride of staff who dressed up for these big events like we almost couldn't recognize them, and I was touched to receive the many compliments from guests expressing how impressed they were. But we haven't finished yet. Rev. Fr. Louis Ha and his team in the Centre for Catholic Studies, CUHK, is working on a book on SPH History, which is going to be published soon.

These celebratory events are not only meant for the past. For one, they helped to build teamwork among internal departments, and forge better links with our visiting doctors and the community. They also serve as an opportunity for us to reflect upon our hospital mission and journey. I found the History Book project most illuminating. Rather than just doing a chronological recount, Fr. Ha boldly undertook to juxtaposition the development of SPH with the evolution and changes of the healthcare system in Hong Kong, which itself is subject to the bigger social, economic and technological developments. One then comes to appreciate how SPH had been constantly adapting to these tides of change, overcoming challenges and excelling all the way.

The present situation is no different. To date, the Government just finished consultation over its new proposal to tighten regulation on private healthcare facilities, as well as the Voluntary Health Insurance Scheme, and is entering into the legislative process. Meanwhile, the clout of the health insurance trade in influencing healthcare practice is already being felt. On top of that, the expansion of private hospital beds lately is unparalleled in decades, signifying more intense competition for customers and experienced staff. At the same time, staff shortage for certain grades seems to be a global problem for both the public and private sectors. All these call for careful navigation – and this is just half the story.

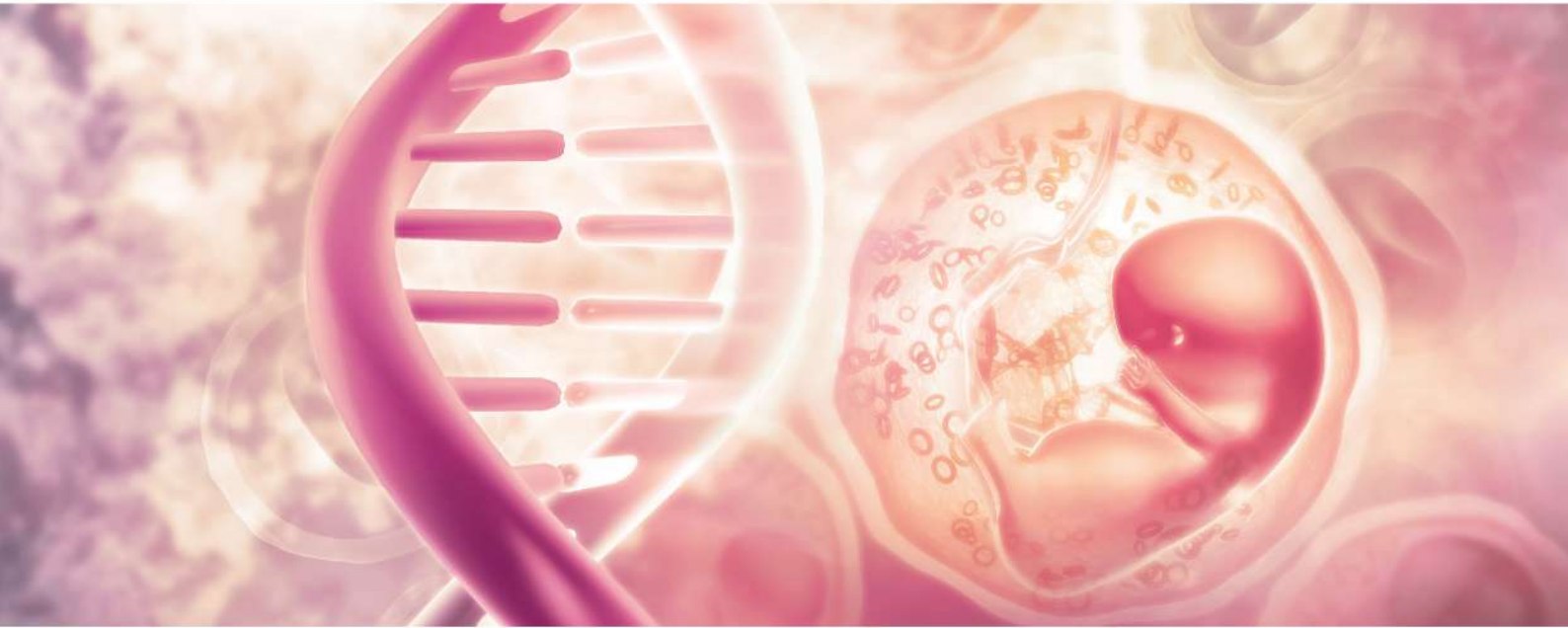
In healthcare we are not merely talking about business. Good clinical care involves proper governance, teamwork, an atmosphere of continuous learning and improvement, and evidence-based audits and performance reviews. SPH has just gone through the Organization Wide Survey of ACHS in May, with all criteria satisfied and all previous recommendations closed. There will be new recommendations, including improvement of visiting doctors' compliance to hospital policies on Hand Hygiene and medical record documentation. We are most grateful for the enthusiastic participation of resident and visiting doctors on our various Clinical Advisory Committees and Quality Assurance Meetings to drive clinical improvements.

We receive patient feedback every day from the Hospital Services Satisfaction Survey. While I feel good in reading compliments on our new building and facilities, I am much more heartened by positive comments on the quality of clinical service and holistic care, that we are truly living up to the hospital mission and values.

Let's keep up the good work!



Clinical use of non-invasive prenatal tests (NIPT)



Prenatal screening for common aneuploidies has traditionally been carried out in the form of ultrasound, maternal serum screening or a combination of the two. In recent years, newer non-invasive tests become commercially available for prenatal screening by sequencing of cell-free DNA (cfDNA) in the maternal circulation, commonly known as NIPT. NIPT has almost replaced invasive diagnostic tests for prenatal fetal sex and blood group determination, due to its high accuracy. This article is focused on the use of NIPT for detecting chromosomal abnormality.

The primary source of fetal cfDNA in the maternal circulation is from the placenta (syncytio-trophoblasts), while fetal erythroblasts constitutes a smaller portion. Although fetal cfDNA becomes detectable in maternal blood from 5 gestational weeks onwards, an adequate fetal fraction (>3-4% of total maternal cfDNA) is usually obtained after 10 gestational weeks. Therefore, most laboratories carry out NIPT ≥ 10 gestational weeks.

NIPT is the most sensitive screening test for common aneuploidies, namely trisomy 21, 18 and 13 and sex chromosome aneuploidies. NIPT remains as screening tests due to its lower sensitivity and specificity when compared to invasive diagnostic procedures with karyotyping, e.g. amniocentesis and chorionic villous sampling.

	Detection rate (%)	False positive rate (%)
Trisomy 21	99.5 (95% CI 0.983–0.998)	0.05
Trisomy 18	97.7 (95% CI 0.952–0.989)	0.04
Trisomy 13	90.6 (95% CI 0.823–0.958)	0.06
Monosomy X	92.9 (95% CI 0.741–0.984)	0.23

False positive cfDNA results, i.e. fetus unaffected, but cfDNA tests indicates aneuploidies can result from:

- Confined placental mosaicism: where the abnormal chromosomes are confined only to the placenta.
- Demised twin

Rarely:

- Maternal mosaicism and maternal copy number variants
- Maternal cancer: In a pregnant woman with a tumor, cell free fetal and maternal DNA and tumor DNA contribute to total cfDNA

Falsely negative cfDNA results are also possible due to

- Confined placental mosaicism: where the placenta of an aneuploidy fetus has normal chromosomes
- Borderline low fetal fraction: e.g. 3-5%
- Technical issues

NIPT remains therefore as a screening test for aneuploidies. In the context of a positive result, invasive diagnostic procedure with conventional karyotype +/- microarray is necessary to confirm the diagnosis. Amniocentesis has the advantage of obtaining genuine fetal cells and excludes the possibility of placental mosaicism.

NIPT does not test for all genetic syndromes or all aneuploidies. In case there are one or more structural anomalies on ultrasound examination, direct invasive diagnostic procedure with full karyotype and microarray should be considered, even when NIPT screened negative.

With advancement in laboratory techniques and information on human genomes, cfDNA will likely provide more information and become more affordable. Although not recommended by all professional authorities, NIPT can technically detect microdeletion/microduplication syndromes, single gene disorder, etc. It is therefore of utmost importance women receive appropriate pre-test counselling, so that they can make informed choices regarding the test they want or need.

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Bronchoscopic Lung Volume Reduction

Chronic obstructive pulmonary disease which is characterized by persistent respiratory symptoms and airflow limitation is the fourth leading cause of death in the world. Medical treatment includes smoking cessation, vaccination, bronchodilators use together with pulmonary rehabilitation. Lung volume reduction surgery (LVRS) is a surgical treatment for patients with advanced emphysema whose symptoms cannot be controlled by medical treatment. It improves pulmonary function and exercise capacity. However, surgical morbidity is high and non-pulmonary comorbidities may preclude surgery.

Bronchoscopic lung volume reduction (BLVR), a technique to treat hyperinflation due to emphysema via flexible bronchoscope, offers a less invasive approach to lung reduction. After treatment the hyperinflation, the work of breathing will decrease and the remaining lung tissue will have normal elastic recoil pressure. BLVR includes a variety of different bronchoscopic procedure, including endobronchial valve, coil etc., to collapse areas of overinflated emphysematous lung.

The Global initiative for Chronic Obstructive Lung disease (GOLD) report recommended the use of BLVR in selected patients with advanced emphysema since 2017. (1) Before considering BLVR, patient should receive optimal medical therapy, have completed or are undergoing pulmonary rehabilitation. Evaluation includes complete lung function measurements, computed chest tomography and a 6 minute walk test.

Valves:

One way valves, which allow air and mucous to exit the treated area, but not allow air to re-enter, have been decided to treat hyperinflation. Two types of valves, endobronchial valve (EBV, Zephyr, Pulmonx) and intrabronchial valve (IBV, Spiration, Olympus), have been studied.

A large prospective multicenter RCT of endobronchial valve placement showed statistically significant improvement in FEV1 (6.8 %, 95% CI 2.1-11.5) and 6 minute walk distance (5.8%, 95% CI 0.5-11.2)



compared to control group. In patient with severe heterogeneous emphysema compared to control therapy at 6 months post intervention. (2) Patients who have heterogeneous emphysema with complete fissure have greater improvement in FEV1 and 6-minute walk test. (3) FEV1 increased by a median 8.77% compared to baseline in the EBV group versus 2.88% in the control group.



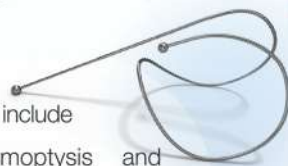
Regarding intrabronchial valves, the efficacy and safety profile are limited by small number of RCTs. A multicenter, prospective, open enrollment cohort study shows significant improvement in quality of life by measurement of St George's Respiratory Questionnaires, but no significant improvement in physiological testing.(4)

Identification of collateral ventilation and fissure integrity significantly improve the efficacy of EBV. The Chartis System is an assessment tool to determine the presence of collateral ventilation. The balloon catheter is advanced during bronchoscopy into the target lobe and measures the expiratory air flow, resistance and pressure to identify which patients have minimal to no air flow. Combining CT-fissure integrity with the Chartis system, one can identify those patients who are most likely to respond to valve placement.

Complications of valves placement include COPD exacerbation with hospitalization, hemoptysis and pneumothorax.

Coil:

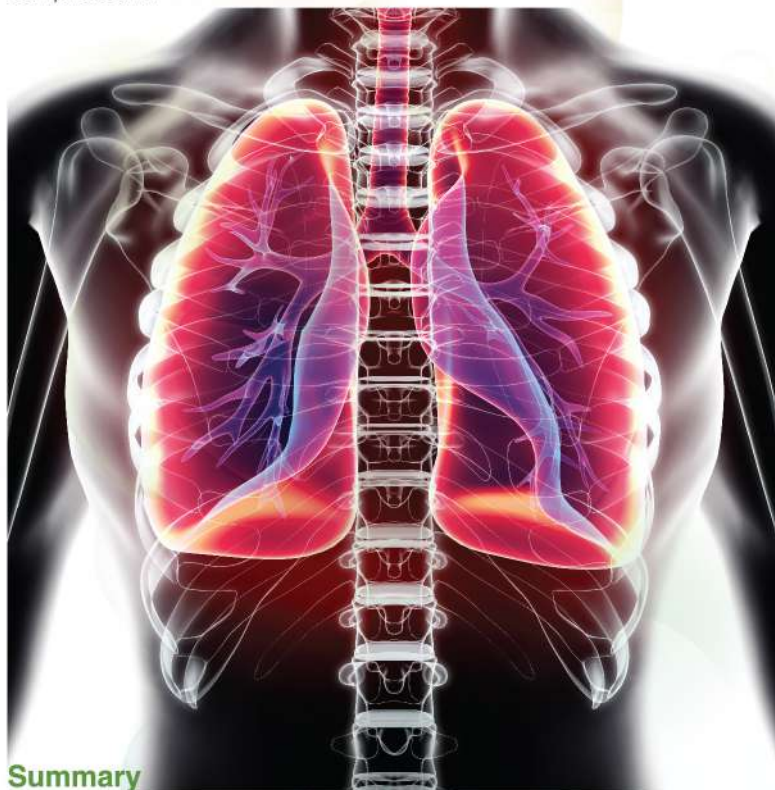
Endobronchial coil therapy (PneumRx, Inc. Mountain View) is a non-blocking partially irreversible treatment that is independent of collateral ventilation. The deployment of coils results in collapse and compression of the lung tissue in that area. Compared to valves placement, Coils are effective in both heterogeneous and homogenous emphysema, independent of collateral ventilation. In a multicenter trial, 100 patients with severe emphysema (included both heterogeneous and homogenous), 36% of the coil group experienced more than a 54m improvement in the 6-minute walk distance, compared with 18% in the control group. (5) However, there is study suggested a gradual waning benefit of coils after 1 year.



Major complications of Coil therapy include pneumonia, COPD exacerbation, hemoptysis and pneumothorax. Some of reported patients complicated with hemoptysis required bronchial artery embolization.

Other techniques:

Thermal airway ablation is a technique by using heated vapor to induce local inflammatory reaction that results in fibrosis, scarring and shrinkage of the target area. A multinational, multicenter randomized controlled trial evaluated patients with upper lobe predominant emphysema. There was 14.7% improvement in FEV1 between the treatment groups versus the control group. (6) Biologic lung volume reduction uses direct application of a sealant/remodeling system to collapse areas of emphysema. Though study demonstrated improvements in FEV1 and mMRC, there was significant proportion of patients (44%) experienced complications.



Summary

Patients with advanced emphysema who have failed maximal medical therapy and not smoking should consider for lung volume reduction. Chest CT imaging to assess fissure completeness and collateral ventilation can further determine the respond to therapy. Patient with heterogeneous emphysema with collateral ventilation, surgical LVRS maybe better choice. But patients without collateral ventilation, endobronchial valves maybe considered. Coils may be considered in the patient with homogenous emphysema.

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Cytochrome P450 Enzymes in Drug Interactions

SPH Pharmacy Department

The following clinical scenario describes a case of drug interaction:

A 70-year-old woman taking warfarin 2mg daily, whose INR was well controlled with consistent diet, has recently noted difficulty in maintaining the desired therapeutic level. The medication review showed that a weekly fluconazole therapy was prescribed by a clinic doctor recently for patient's recurrent vulvovaginal candidiasis infection. Her cardiologist suspected the potential drug interaction between warfarin and fluconazole causing the increase in her INR and replaced fluconazole with an alternate topical antifungal agent. The patient's INR quickly resumed to therapeutic range.

Introduction

Drug interactions are preventable causes of patient harm. Potential detrimental care to patient may occur due to either increased drug effect causing toxicity or decreased drug effect leading to suboptimal treatment. Drug-drug interactions are significant as they cause 10 to 20% of the adverse drug reactions requiring hospitalization which are preventable¹. Knowing how drug-drug interactions occur and how to manage them is an important part of clinical practice. Many adverse drug-drug interactions are attributable to the pharmacokinetic aspect and can be understood in terms of alterations of cytochrome P450 (CYP450) catalyzed reactions.

CYP450 Metabolism

The CYP450 family includes 56 different functional enzymes, in which, 6 of them (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5) participate in the metabolism of over 95% of commonly used drugs². The CYP450 enzymes are predominantly expressed in the liver, but are also found in the small intestine, lungs, placenta and kidneys³.

Drugs interact with the CYP450 system in multiple manners. Drugs may be metabolized by only one CYP450 enzyme (e.g. metoprolol

by CYP2D6) or by multiple enzymes (e.g. warfarin by CYP1A2, CYP2D6, CYP2C9 and CYP3A4)^{4,5}. Drugs that cause CYP450 metabolic drug interactions are referred to as either inhibitors or inducers (Table 1). Inhibitors obstruct the metabolic activity of one or more CYP450 enzymes. The extent of an inhibitor affecting the metabolism of a drug depends on various factors such as the dose and binding affinity to the enzyme. For example, sertraline is a mild inhibitor of CYP2D6 at a dose of 50 mg, but if the dose is increased to 200 mg, it is considered a potent inhibitor⁶.

Inducers promote CYP450 enzyme activity by increasing enzyme synthesis. Depending on the half-life of the inducers, there is usually a delay before enzyme activity increases. For example, reduction in concentration of a drug which is a CYP2C9 substrate can occur within 24 hours after the initiation of rifampin which is an inducer with short half-life (3-4 hours)⁷. Coherently, the decrease in concentration of the same drug substrate can occur up to a week after the initiation of phenobarbital, which is an inducer with a long half-life (53-118 hours)^{8,9}. A drug may also be metabolized by the same CYP450 enzyme that it induces, known as auto-induction. Carbamazepine, a potent CYP3A4 inducer and substrate, should be initiated at a low dose and then increased at weekly intervals as its half-life gradually decreases over time to minimize the risk of concentration-dependent toxicity.

Some drugs rely on CYP450 enzymes for conversion to their active form. Inhibition of conversion from prodrug to active drug may lead to inadequate concentration of the active drug and therapeutic failure. For example, tamoxifen is metabolized by CYP2D6 to its active form endoxifen, and concomitant use with paroxetine (strong CYP2D6 inhibitor) has been associated with increased mortality in breast cancer¹⁰.

Enzyme	Inhibitor*	Inducer	Substrate
CYP1A2	ciprofloxacin, fluvoxamine , ethinylloestradiol, interferon alfa-2b	phenobarbital, phenytoin, tobacco	amitriptyline, haloperidol, olanzapine, ondansetron, propranolol, theophylline, warfarin
CYP2C9	amiodarone, fluconazole, fluoxetine	carbamazepine, rifampin	celecoxib, gliclazide, ibuprofen, tamoxifen
CYP2C19	fluconazole, fluvoxamine , fluoxetine, clarithromycin, voriconazole, moclobemide	carbamazepine, rifampin	omeprazole, phenobarbital, phenytoin
CYP2D6	bupropion, fluoxetine, paroxetine , cinacalcet, doxepin, duloxetine, flecainide, moclobemide, quinine, sertraline, terbinafine	no significant inducer	amitriptyline, carvedilol, codeine, donepezil, metoprolol, paroxetine, risperidone, tamoxifen, tramadol, warfarin
CYP3A4 & CYP3A5	macrolides e.g. erythromycin, clarithromycin azole antifungals e.g. voriconazole, itraconazole, ketoconazole non-dihydropyridine calcium channel blockers e.g. diltiazem, verapamil grapefruit juice , aprepitant, cimetidine, ciprofloxacin, cyclosporin, fluvoxamine	carbamazepine, St. John's wort, phenobarbital, phenytoin, rifampin	alprazolam, amlodipine, aprepitant, atorvastatin, cyclosporine, estradiol, simvastatin, sildenafil, verapamil, warfarin, zolpidem

Table 1| Significant Cytochrome P450 Enzymes and Examples of Inhibitors, Inducers, and Substrates^{4,5}
(* bold font indicates strong inhibitors)

Here is another clinical scenario describes a case of drug interaction:

A 75-year-old male consulted a gastroenterologist for *H. Pylori* infection, and triple therapy including oral clarithromycin, amoxicillin and pantoprazole were prescribed to patient for 14 days. He was taking simvastatin for his hyperlipidemia. Patient complained of unusual muscle pain after 10 days of triple therapy. His cardiologist presumed that the concurrent use of clarithromycin and simvastatin might lead to the condition, and withheld simvastatin until he finished the triple therapy. Patient's muscle pain was resolved upon stop taking simvastatin.

Drug Interaction and Adverse Drug Effects

Two commonly prescribed cholesterol lowering medications, simvastatin and atorvastatin, are CYP3A4 substrates. The concomitant use with macrolide antibiotics, clarithromycin and erythromycin, may lead to an increase in the plasma concentration of either statin and increase the risk of adverse drug reactions including myopathy and rhabdomyolysis¹¹. The risk of rhabdomyolysis is estimated at approximately 3.4 cases per 100,000 person-years with standard-dose of statin therapy¹². However, the risk increases with higher therapeutic doses, longer duration and by prescribing statins in combination with strong inhibiting drugs.

Azithromycin may be a safer choice for patients taking the affected statin.

A cohort study shown that the use of clarithromycin or erythromycin in patients aged 65 and over taking atorvastatin, simvastatin or lovastatin was associated with a 2-fold higher hospitalization risk with rhabdomyolysis when compared with those prescribed with azithromycin. However, if use of the potent CYP3A4 inhibitor is unavoidable, depending on patient's clinical condition, the affected statin may be considered to withhold during the duration of therapy¹³.

Conclusion

Most potential drug interactions can be recognized by understanding the pharmacology behind the interactions. It is crucial to collect and review patient's completed medication history to aid in drug selection. When prescribing drugs which are inducers or inhibitors of CYP P450 enzyme, healthcare professionals should alert and increase vigilance to identify unwanted drug interactions before they cause significant harm. A switch of the target drug may need to be considered to reduce the possibility of drug-drug interactions. Or else, dose adjustment may be attempted to minimize the possible alteration in drug metabolism, accompany with close monitoring of the clinical conditions of the patient.

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The following drugs are approved for use in St. Paul's Hospital (SPH) following Drug and Therapeutics Committee meeting in May 2018

Drugs	Indication	Usual dosage	Remarks
Nexium (Esomeperazole) 10mg sachet of granules for oral suspension	Treatment of GERD in children 1-11 years old.	<ul style="list-style-type: none"> Treatment of endoscopically proven erosive reflux esophagitis: Weight $\geq 10\text{kg}$ --<20kg: 10mg daily for 8 weeks Weight $\geq 20\text{kg}$: 10 to 20mg daily for 8 weeks Symptomatic treatment of gastroesophageal reflux disease (GERD): 10mg daily for up to 8 weeks 	Each 10mg sachet granules to be dispersed into 15mL of water. Drink within 30minutes. Can also be administered through enteral feeding tubes. <u>On special request only.</u> Please contact Pharmacy Department.
Matrixam (Indapamide SR 1.5mg/ Amlodipine 5mg & 10mg) modified-release tablet	Substitution therapy for treatment of essential hypertension in patients already controlled with indapamide and amlodipine given concurrently at the same dose level.	One tablet per day, preferably in the morning.	-
Zerbaxa 1.5g (Ceftolozane 1g/Tazobactam 0.5g) injection	<ul style="list-style-type: none"> Treatment of complicated urinary tract infections (cUTI), including pyelonephritis. In combination with metronidazole is indicated in adult patients for the treatment of complicated intra-abdominal infections (cIAI). 	1.5g every 8 hours by IV infusion over 1 hour.	<u>On special request only.</u> Please contact Pharmacy Department.



CME

ANNOUNCEMENT

CME/CPD/CNE Programme 2018

Reproductive Genetics and Recent Advances

Speaker: Dr. LEE Chi Yan, Vivian

Specialist in Obstetrics & Gynaecology

Chairman: Dr. LAW Chi Lim, Robert

Honorary Consultant in Obstetrics & Gynaecology, SPH

Date: 13 September 2018 (Thursday)

Time: 7:00 pm – 7:30 pm Reception (light refreshment provided)
7:30 pm – 8:30 pm "Reproductive Genetics and Recent Advances"
by Dr. LEE Chi Yan, Vivian
8:30 pm – 9:00 pm Q&A session

Venue: Meeting Room, 2/F, Block B, St. Paul's Hospital

Registration & Enquiry:

(First-come-first-serve)

Contact Person: Ms. Jackie Tang

Tel: 2830 3904, Fax: 2837 5271,

E-mail: sph.sdd@mail.stpaul.org.hk

CME / CPD / CNE Accreditation for all Colleges (Pending approval)

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