Fasting before lipid tests: An absolute requirement?

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Fasting before lipid tests: An absolute requirement?

Rajesh Kumar

Fasting prior to routine blood lipid tests may be unnecessary, according to new research.

The findings have stirred a debate, with some physicians proposing to do away with the current guidelines that recommend measuring fasting lipid levels, while others are advising caution.

Earlier studies have suggested that non-fasting lipid profiles change minimally in response to food intake and may be superior to fasting levels in predicting adverse cardiovascular outcomes, said study authors Drs Davinder Sidhu and Christopher Naugler of the University of Calgary, Alberta, Canada. [Arch Intern Med 2012;172:1707-1710]

To confirm the findings in a large community cohort, they conducted a cross-sectional examination of laboratory data from 209,180 subjects, of whom 111,048 were women. The data included records of the subjects’ fasting durations, which ranged from 1 to 16 hours, and their lipid level measurements, over a 6-month period in 2011. Fasting time was stratified into hourly intervals from 1 to 16 and correlated with lipid results including mean high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol (TC), and triglycerides (TG).

On analysis, the researchers found that the mean levels of TC and HDL cholesterol differed little between individuals with various fasting times. Specifically, these levels varied by less than 2 percent for TC and HDL cholesterol, less than 10 percent for calculated LDL cholesterol, and by less than 20 percent for TG.

“This finding suggests that fasting for routine lipid level determinations is largely unnecessary,” said the researchers.

In an accompanying editorial, Dr. J. Michael Gaziano of Brigham and Women’s Hospital, Harvard Medical School in Boston, Massachusetts, US, said the incremental gain in information of a fasting profile is exceedingly small for total and HDL cholesterol values and likely does not offset the logistic impositions placed on our patients, laboratories, and our ability to provide timely counseling to our patients.

“This, in my opinion, tips the balance toward relying on non-fasting lipid profiles as the preferred practice. Therefore, in practice, you can begin with a non-fasting lipid profile and [use it] for risk assessment, decisions about treatment and monitoring the effects of treatment,” Gaziano concluded, adding that some sample fasting may be useful.

Drs Amit V. Khera and Samia Mora, also of Brigham and Women’s Hospital and Harvard Medical School, in their commentary, said that “a growing body of evidence from observational studies and statin clinical trials suggests that non-fasting or fasting blood draws may be used for cardiovascular risk assessment and therapeutic decisions, especially when lipid sub-fractions other than LDL-C (eg, the total HDL-C ratio or non-HDL-C) are emphasized.”

“Additional prospective studies that directly compare the association of fasting and non-fasting lipid levels with cardiovascular outcomes in the same individuals would be informative. Further validation studies are needed before a non-fasting lipid testing strategy is universally endorsed,” wrote Khera and Mora.
Dr. Ho Kay Woon, cardiologist at the National Heart Centre Singapore, said that central to interpreting the study results is the premise that LDL is the primary target of treatment, as demonstrated in multiple, large, randomized trials and subsequent guidelines.

However, LDL value is not directly measured in the common biochemistry laboratory but is derived using the formula: \( \text{LDL} = \text{TC} - \text{HDL} - \frac{\text{TG}}{5} \).

“In subjects with TG levels more than 400mg/dL, LDL estimation by this method is not accurate. Of note, Sidhu and Naugler’s study excluded 1.5 percent of patients who had TG levels [higher] than 400 mg/dL, many of whom may be a result of not fasting before lipid testing,” said Ho.

“As diet affects TG levels up to 20 percent, this significantly affects the accuracy of the derived LDL levels if a subject has not fasted. Indeed in this study, the variability of LDL with fasting can up around 10 percent. When taken in context that LDL needs to be closely monitored and treated to target, this variability of LDL without fasting does not provide a precise measurement for lipid management.”

Therefore, although the study showed interesting results with potential application of non-fasting lipid measurements, Ho did not foresee a change in the requirement for fasting lipid sample to accurately determine the LDL levels, which remains the current primary lipid treatment target.
The number of preterm births in 39 high-resource countries can be reduced with some readily available treatments, and this could result in preventing 58,000 premature babies a year, says a group of international experts.

Preterm birth, defined as delivery before 37 weeks of completed gestation, is the leading cause of newborn deaths. Babies who survive early birth often face a lifetime of health challenges, including breathing problems, cerebral palsy, and motor and intellectual disabilities.

In addition to preventing preterm births, the economic cost-savings to the healthcare system could number in the billions. “Governments and health professionals in these 39 countries need to know that wider use of proven interventions can help more women have healthy pregnancies and healthy babies,” said lead author Dr. Hannah H. Chang, a consultant for The Boston Consulting Group (BCG), Boston, US. “A 5 percent reduction in the preterm birth rate is an important first step.”

The article was published to coincide with the second annual World Prematurity Day. [Lancet 2012 doi:10.1016/S0140-6736(12)61856-X]

The authors listed five proven interventions which, when combined, could lower the rate of preterm births across the 39 countries from an average 9.6 percent of live births to 9.1 percent, and save about US$3 billion in health and economic costs:

- eliminating early cesarean deliveries and induction of labor unless medically necessary.
- decreasing multiple embryo transfers during assisted reproductive technologies.
- helping women quit smoking.
- providing progesterone supplementation to women with high-risk pregnancies.
- cervical cerclage for high-risk women with short cervix.

“The means to reduce the risk of preterm birth by 5 percent are already available,” said Dr. Catherine Y. Spong, associate director for extramural research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, US. “Continued research into the causes of preterm birth has the potential to reduce the proportion of infants born preterm even further.”

The significance of the 5 percent reduction builds on recommendations of the publication Born Too Soon: The Global Action Report on Preterm Birth, which presented the first-ever preterm birth data for 184 countries and outlined steps that all countries could take to help prevent preterm births and care for affected newborns.

About 15 million babies worldwide are born preterm each year and more than one million of these die as a direct result of their early birth. The US preterm birth rate ranks 131 out of 184 countries. [Born Too Soon: The Global Action Report on Preterm Birth. Available at: www.who.int/pmnch/media/news/2012/preterm_birth_report/en/index.html Accessed on 20 November]
Connecting the wireless health industry

Excerpted from a presentation by Mr. John Stefanac, president of Qualcomm (South East Asia/ Pacific), during the first Asia-Pacific Health Forum recently organized by ESSEC business school in Singapore.

More people today have access to a mobile device than they have to drinking water, electricity or a toothbrush. Or dare I say proper medical care.

Think about the way we acquire and read books today compared with how we did 20 years ago. An average book holds just over 1MB of fixed data, with no access to new data. However, a Kindle can store over 3GB (ie, 3,000 times more data). Think of the way we purchase, listen to and share music, or even the way we search for and book travel compared with how we did 2 decades ago. And think of all of these capabilities finding their way into health care, an industry that to date is virtually untouched by the digital revolution.

Health care is witnessing a big shift from what we call ‘sick care’ to ‘health management care.’ Current healthcare systems pay physicians, hospitals and caregivers for treating sick patients, while the future reimbursement models will pay healthcare institutions and caregivers to keep people healthy and out of acute care settings. This shift in reimbursement models will keep patients healthier and significantly lower health care costs. And mobile health (mHealth) technology will play a huge role in this transformation.

One of the first examples of this shift is that from October 1, 2012, hospitals in the US are being held financially responsible for patient readmissions within 30 days. The ‘Medicare 30-Day Readmission Rule’ is causing hospitals and healthcare facilities to look seriously at remote monitoring technologies to ensure their patients aren’t returning after being discharged.

This creates an opportunity for companies with mHealth solutions to engage with hospitals that earlier didn’t have a huge incentive to listen. Over the past few years, we have been helping to build an mHealth ecosystem by...
connecting the big companies, insurance providers, pharmaceutical and medical device manufacturers, and technology corporations together.

A US$100 million Qualcomm Life Fund has also been set up to accelerate wireless health services and technology adoption. Investments will include:

- biosensors or devices for vertically focused applications like chronic disease care, medication compliance, and fitness or wellness;
- integrated system providers that do remote diagnosis, monitoring, or specialize in enabling independent living;
- software health IT applications; and
- health informatics/analytics.

But it’s also important for startups and innovators to challenge the way things are done in health care. Already, innovative solutions have begun emerging that will help people stay healthy while facilitating easier management of chronic diseases – with seamless access to patient data for all those involved in care.

But there are still some issues that we need to overcome if we are going to see a successful mHealth industry. These include: lack of standards and interoperability; multiple radios and operating systems; the devices’ poor battery life and security concerns. The 2net platform is addressing some of those challenges. The 2net Hub is a plug-and-play wireless gateway device that connects medical devices to ‘cloud’ computing resources seamlessly and can address the complexity of multiple radios and operating systems.

It can push medical device and application data onto the cloud-based internet data repository so that data can be sent securely anywhere it needs to go, be it to the hospital or family physicians. It can support Bluetooth, Bluetooth low energy, Wi-Fi, and ANT+ local area radio protocols which cover the majority of low-power radio medical devices currently used.

By including all of these protocols, the hub alleviates the burden on health service providers of selecting medical devices with only one type of radio. To meet healthcare security and privacy requirements, data will be communicated using SSL secure communication and separately certified as Class-1 Medical Devices under the EU Directive 93/42/EEC (MDD) and US FDA listed as Class I Medical Device Data Systems (MDDS).

At the individual level, we will soon use our phones to communicate, manage our time, pay our bills, turn the thermostat at home on to the appropriate temperature as we’re leaving work, open our door when we get home, and, we believe, to eventually manage and even diagnose our health with a new world of Internet of Medical Things.

New healthcare tools are now available that leverage wireless and mobility to allow consumers to take charge of their own health. Some examples are:

- Entra’s MyGlucoHealth Bluetooth blood glucose meter that allows diabetics to transmit their blood sugar readings to the cloud-based internet data repository to better manage their disease;
- Asthmapolis wirelessly enabled asthma inhaler;
- Lifecomm 3G-enabled personal emergency response device to monitor the elderly, including motion sensors and voice recognition and location capabilities; and
- A&D Medical’s Bluetooth enabled blood pressure cuffs, weight scales, and other health-related devices to manage chronic diseases and wellness.

The time is truly ripe for a mobile healthcare revolution.
Fast food a possible culprit behind asthma and allergies

Christina Lau

Children who consume fast food frequently have an increased risk of asthma and allergies, according to results of an international study presented at the 17th Congress of the Asian Pacific Society of Respirology held recently in Hong Kong.

The ISAAC study (International Study of Asthma & Allergies in Childhood) was conducted in three phases to assess the prevalence and severity of asthma and allergic diseases, possible risk factors, and time trends in the prevalence and severity of these conditions in nearly 2 million children in more than 100 countries.

“Latest data from phase 3 suggest that frequent consumption of fast food is associated with increased risk of asthma, rhinoconjunctivitis and eczema in children aged 13-14 years,” said Dr. Christopher Lai, Honorary Clinical Professor at the Chinese University of Hong Kong. [Ellwood P, et al. Thorax, in press]

The association was observed in all ISAAC phase 3 centers. In the Asia-Pacific region, children who consumed fast food ≥3 times per week had a 21 percent increased risk of current wheeze, 26 percent increased risk of severe asthma, 18 percent increased risk of current rhinitis, 101 percent increased risk of severe rhinitis, and 77 percent increased risk of severe eczema.

In contrast, children who consumed fruits ≥3 times per week had a lower risk of asthma. [Ellwood P, et al. Thorax, in press]

While outdoor air pollution may play a role in causing asthma in susceptible individuals living very close to busy roads with a lot of truck traffic, the UK’s Committee on the Medical Effects of Air Pollutants recently concluded that air pollutants are likely to make only a small contribution vs other factors in the development of asthma, and in only a small proportion of the population. [Respirology 2012;17:887-898] Furthermore, a recent study found no evidence of a positive association between ambient air pollution and asthma prevalence as measured at the community level. [Environ Health Perspect 2012;120:1333-1339]

“In Chinese children, the prevalence of asthma appears to be highest in areas with a more western lifestyle of living, and may be
increasing in mainland China and Taiwan while decreasing in Hong Kong,” noted Lai. “Among Chinese adolescents living in mainland China, Hong Kong and Canada, residents of mainland China were least likely to have asthma symptoms. The risk was higher for those living in Hong Kong and those who migrated to Canada, and highest for Chinese adolescents born in Canada. These findings suggest that environmental factors and duration of exposure may affect asthma prevalence.” [CMAJ 2008;179:1133-1142]

Flow diverter promising in treating cerebral aneurysms

Jackey Suen

Pipeline embolization device (PED) placement has shown promising effectiveness in the treatment of cerebral aneurysms, according to a recent study by the Chinese University of Hong Kong (CUHK).

Cerebral aneurysms currently affect about 2 to 6 percent of the Hong Kong population, and have an average risk of rupture of 1.3 percent per year. The rupture may lead to severe disability, and the mortality rate is as high as 45 percent. Although endovascular coil embolization has been accepted as a treatment option, its application is largely limited by unfavorable features of aneurysm such as wide neck, large size, fusiform morphology and post-treatment recanalization. A modified form of coil placement, called stent-assisted coil placement, could overcome the above challenges, but is associated with relatively high rates of aneurysm recurrence and mortality after treatment. [Radiology 2012;265:893-901]

“PED works by diverting blood flow away from the aneurysm so it gradually regresses. It is a tube-like device composed of tightly knitted fine metal strips, designed in such a way to be implanted in the vascular segment affected by the aneurysm using a percutaneous endovascular approach,” explained lead researcher Professor Simon Yu of CUHK’s Vascular and Interventional Radiology Foundation Clinical Science Center, at a press conference. “In our prospective non-randomized multicenter study, we evaluated the efficacy and safety of PED placement as a new treatment option for cerebral aneurysms in 143 patients with a total of 178 aneurysms.”

Patients in the study had unruptured saccular or fusiform aneurysms or recurrent aneurysms after previous treatment. PED placement was successful in all aneurysms, with most cases (81.5 percent) requiring only one device in each aneurysm.

“At 6-month follow-up, complete occlusion was found in 55.7 percent of aneurysms. The occlusion rate increased to 81.3 percent at 12 months and 84.5 percent at 18 months,” reported Yu.

In the study, peri-procedural death or major stroke occurred in 3.5 percent of the cases. No parent artery occlusions were found in the follow-up period. Mild (20-30 percent) parent artery stenosis and side branch occlusion occurred in 1.4 percent of the cases with
no clinical consequences.

“Our findings suggest that PED is a reasonably effective and safe treatment for cerebral aneurysms. The treatment is promising for aneurysms with unfavorable morphologic features, and should be considered a first choice for unruptured aneurysms and recurrent aneurysms after previous treatments,” Yu suggested.

A major concern of PED placement is delayed occlusion, the reasons of which remain unclear. This inability to immediately occlude the aneurysm contributes to risk of rupture during the latency period. According to the CUHK researchers, concomitant endosaccular coil placement may be a reasonable strategy to prevent post-treatment aneurysm rupture.

According to a recent review, other concerns are delayed clinical outcomes after PED treatment, including cases of ischemic events and parent artery ruptures. [EJMINT Original Article;2012:1225000057]

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**Setting quality standards for TCM ingredients**

**Naomi Rodrig**

The Department of Health (DH) recently published new reference standards for 42 herbs commonly used in traditional Chinese medicine (TCM).

Research on the safety and quality of herbal ingredients – also known as Chinese Materia Medica (CMM) – is in line with government policy to establish accepted standards on herbs commonly used in Hong Kong. With the latest batch, the number of CMM items covered in the Hong Kong Chinese Materia Medica Standards (HKCMMS) has reached about 200.

The publication lists the names, sources and descriptions of the herbs, as well as identification methods such as microscopic examination, thin layer chromatography and high-performance liquid chromatographic fingerprinting.

Herbal ingredients are selected for research and inclusion in the HKCMMS based on their common usage in the local community, international concern regarding their safety and quality, and economic value.

“In parallel with the growth of Chinese herbal medicine, there is a challenge to establish quality control standards for commonly used CMM. In providing a stronger evidence-based reference on the safety and quality of herbal medicines, the HKCMMS helps to address safety and quality issues such as contamination with heavy metals and other contaminants,” a DH spokesman remarked.

The research work is conducted at six local universities, while an International Advisory Board comprising local, mainland and overseas experts advises on the research principles, methodologies and analytical techniques. Mainland regulatory authorities, including the State Food and Drug Administration and the State Administration of TCM, also provide advice and support for the project.
Children with obstructive sleep apnea (OSA) are at increased cardiovascular (CV) risk, but the risk can be reduced if OSA is resolved, a local study suggests.

Researchers from the Chinese University of Hong Kong (CUHK) followed nearly 200 children (age, 6-13 years) for 4 years to investigate associations between childhood OSA and blood pressure (BP) levels.

Results, presented recently at the 17th Congress of the Asian Pacific Society of Respirology in Hong Kong, showed that children with obstructive apnea-hypopnea index (OAHI) >5/hour at baseline had significantly higher daytime and nighttime BP at both baseline and 4-year follow-up. “These children also had a significantly higher rate of nocturnal prehypertension at 4 years vs those with baseline OAHI <1/hour,” reported Professor Albert Martin Li of the Department of Pediatrics.

“The ‘10 billion dollar’ question of whether childhood OSA will progress to adult OSA remains unknown because follow-up studies on this important childhood condition are scarce in the current scientific literature,” he continued. “However, we showed that most children with OSA at baseline still had OSA at 4-year follow-up.”

Among children with baseline OAHI >5/hour, 88 percent still had OSA at 4-year follow-up (OAHI 1-5/hour, 32 percent; OAHI >5/hour, 56 percent). In those with baseline OAHI of 1-5/hour, OSA persisted in 59.1 percent at 4 years (OAHI 1-5/hour, 45.5 percent; OAHI >5/hour, 13.6 percent).

“Importantly, those with OSA resolved after 4 years had a significant reduction in night-time systolic BP z score compared to those in whom OSA persisted,” said Li. “Change in OSA severity was associated with BP levels and nocturnal prehypertension at 4 years.”

According to Li, the findings reinforce the importance of diagnosing and treating childhood OSA early. “Early and effective treatment can reverse a great proportion of potential complications,” he stressed. “However, in a number of children treated with adenotonsillectomy, especially in obese children, there will be residual or recurrent OSA. More longitudinal studies are required to provide better understanding of the natural history of childhood OSA.”
Hospital tax scrutinized

Naomi Rodrig

The Hong Kong-based insurance provider Kwiksure announced it will investigate whether some private hospitals operated by nonprofit religious organizations have abused their tax privileges.

The private charity hospitals are currently exempt from tax payment on the premise that they are involved in charitable work, but these terms may have been violated, according to local press reports. The insurer is now calling for a closer examination and a potential revocation of tax exemptions for violators.

While the annual profits of the private hospitals are estimated at HK $400 million, external monitoring has been lax, and many are questioning whether additional taxes ought to be introduced given the government’s large fiscal reserves.

Kwiksure’s investigation follows recent demands from LegCo to examine whether the charity hospitals are indeed doing charitable work, as well as calls from the general public for stricter monitoring of the private hospitals’ business practices.

Resveratrol restores stem cells in premature aging

Christina Lau

A local study shows that resveratrol, a substance in grapes, restores stem cells and delays the onset of aging in a premature aging disorder known as Hutchinson-Gilford Progeria Syndrome (HGPS).

HGPS is a rare genetic disease characterized by severe premature aging that manifests as early as 6 months after birth. With the aging process accelerated 5-10 times vs normal, patients have an average lifespan of 13 years only. More than 90 percent die from cardiovascular problems such as atherosclerosis.

“HGPS is caused by a mutation in the LMNA gene, which gives rise to a malfunctioning lamin A protein called progerin. Using a mouse model and cells from HGPS patients, we found in 2005 that progerin causes defective DNA repair and increases genomic instability, leading to accelerated aging in HGPS,” said lead researcher Dr. Zhong-Jun Zhou of the Department of Biochemistry, University of Hong Kong. [Nature Med 2005;11:780-785]
In their latest 6-year study, Zhou and colleagues sought to investigate the role of stem cells in HGPS and identify a possible cure for the condition. [Cell Metab 2012;16:738-750]

“We showed that lamin A protein is an endogenous activator of the longevity gene SIRT1. Binding of lamin A protein to SIRT1 is required for SIRT1 activity,” reported Zhou. “In the presence of progerin, however, SIRT1 exhibited reduced association with nuclear matrix and decreased deacetylase activity, leading to rapid depletion of adult stem cells in HGPS mice. The depletion occurred before the appearance of aging.”

Importantly, the team showed that activating SIRT1 could rescue adult stem cells, ameliorate premature aging and extend the lifespan of HGPS mice. “We tested the effects of resveratrol on stem cells in HGPS mice. Results showed that resveratrol enhances the binding between SIRT1 and lamin A to increase SIRT1 activity,” said Zhou. “In HGPS mice, resveratrol treatment rescued adult stem cell decline, slowed down body weight loss, improved trabecular bone structure and mineral density, and significantly extended lifespan by 30 percent.”

Based on the results, Zhou suggested that targeting SIRT1 activity would likely provide a novel therapeutic strategy for HGPS and other aging-associated degenerative diseases. “In normal aging, progerin production increases and the protein accumulates in many tissues, although to a significantly lower level than in HGPS. This suggests that normal aging and HGPS may share common mechanisms,” he explained. “People in Hong Kong have the longest lifespan in the world, and there is an urgent need for basic research on aging, which can hopefully extend healthy lifespan and reduce healthcare costs. A possible direction is to develop drugs mimicking lamin A protein to target SIRT1.”

Wearable treatment for hemiplegic arms

Christina Lau

Researchers at the Polytechnic University of Hong Kong (Poly U) have developed a sensory cueing wristwatch for the treatment of hemiplegic arms due to chronic stroke or unilateral cerebral palsy.

The wristwatch is designed to emit vibrations as sensory cueing signals at fixed intervals. These vibrations remind the patients to move their hemiplegic arms as instructed by a therapist.

According to Dr. Kenneth Fong of the Department of Rehabilitation Sciences who led the research, one of the common problems with recovery after a stroke or in children with cerebral palsy is the learned non-use of an arm. “A proportion of the motor impairment results not from the brain cell damage, but from the learned suppression of
movement of the arm. This makes the patient unable to move or develop the arm further,” he explained.

“We have completed three initial clinical trials in hospitals and in community settings over the last few years,” Fong reported.

In the community-based trials, patients with chronic stroke were asked to wear the sensory cueing wristwatch on their affected arm for 3 hours a day and engage in repetitive task practice for 2 weeks, while school-children with unilateral cerebral palsy were asked to wear the wristwatch for 5 hours a day over a 3-week period to remind them to perform a set of predetermined arm exercises. All participants had significant improvement in using their hemiplegic arms. [Arch Phys Med Rehabil 2011;92:15-23; Clin Rehabil 2013;27:82-89]

“In a randomized controlled trial in hospitals, the sensory cueing wristwatch improved arm functions in patients with stroke and unilateral arm neglect compared with a placebo device,” Fong continued.

The research team has obtained patents for the device in the USA and mainland China. “It is now being used in occupational therapy departments of five public hospitals in Hong Kong,” said Fong. “As the device is small, lightweight, user-friendly and cost-effective, treatment can be carried out at home even in the absence of a therapist’s supervision. This allows patients to practice using their hemiplegic arms more in real life.”

The researchers will look for business and industry partners to further develop the wristwatch device with a better design and a new monitoring system.

Doctor shopping for kids: Risky but common in HK

Naomi Rodrig

Doctor shopping is highly prevalent among parents of children who are subsequently hospitalized with acute conditions, suggesting that parents are unaware of the potential hazards of such behavior, a local study found. [Hong Kong Med J 2013;19:Epub Dec 6]

To assess the prevalence and factors associated with doctor shopping (consulting more than one doctor without referral), investigators from the Department of Pediatrics at the Prince of Wales Hospital interviewed the caregivers of 302 children who were admitted between April and July 2011 through the Accident and Emergency Department.

They found that 53 percent of the respondents engaged in doctor shopping for the illness that eventually required hospitalization. The main reason for seeking medical advice
from several physicians was the persistence of symptoms, reported in 73.3 percent of the children. The only significant clinical parameter associated with doctor shopping was fever (odds ratio, 2.4).

“For patients, doctor shopping poses challenge to the continuity of their care and risks potential adverse drug interactions as a result of different medications prescribed by different doctors,” the authors wrote. “This is particularly important in the pediatric population, which is more susceptible to iatrogenic harm and fatalities from polypharmacy.”

Yet, over 75 percent of the parents were unaware of the possible risks of doctor shopping, which was not associated with demographic characteristics or socioeconomic status. The caregivers’ monthly household incomes were similar to the median household income in Hong Kong, the authors pointed out.

Apart from the health hazards for patients, doctor shopping results in wastage of valuable resources, as tests may be repeated and the same medications given by one doctor may be prescribed again by another or at the hospital setting, causing additional cost.

The prevalence of doctor shopping for pediatric inpatients in Hong Kong was significantly higher than that reported for adults at local government-run general outpatient clinics (40 percent) and specialist clinics (26 percent), or for Canadian pediatric outpatients (18 percent). [Int J Qual Health Care 1999;6:371-381; Soc Sci Med 2006;62:2551-2564; Pediatr Child Health 2001;6:341-346]

The investigators noted, however, that a direct comparison may not be appropriate between outpatients and inpatients or between adult and pediatric populations, adding that a high degree of parental anxiety is a probable reason.

Other contributing factors may be differences in healthcare delivery patterns, as well as Hong Kong’s “endemic culture of consumerism supported by the wide array of available healthcare services”, the authors speculated.

“Further measures should be taken to educate subjects on the associated dangers of this behavior and the natural course of acute illnesses with fever,” they recommended.

Flu vaccine uptake remains low

Jackey Suen

Despite alerts on a flu epidemic in the USA and increasing influenza activity in Hong Kong, local uptake of vaccination has remained low, which may be attributed to a lack of knowledge about influenza and influenza vaccination, as shown in a recent survey.

The uptake of influenza vaccination has remained suboptimal at 10 percent. Hence, the Hong Kong Medical Association (HKMA) commissioned a survey from the Public Opinion Program of the University of Hong Kong to assess the public’s awareness of and opinions on influenza vaccination.

A total of 1,013 eligible respondents were interviewed via telephone. Results showed that misconceptions were common regarding the physical harm and preventive measures of influenza, and the importance of influenza vaccination.
For example, 85.6 percent of the respondents did not get influenza vaccination in the past year; 25 percent of them believed they were in good health, indicating that they might have overestimated their ability to fight against influenza. Only about 3.4 percent knew that influenza accounted for more than 300 cases of ICU admission or death in Hong Kong between January and July 2012. “This shows that the public has underestimated the harm of influenza to individuals and the society,” explained the HKMA spokesman.

Over 80 percent of the respondents did not know about herd immunity, and less than 10 percent knew that it takes 2 to 4 weeks to develop immunity after vaccination. Furthermore, only 68.4 percent of the respondents knew that vaccination is the most effective means to prevent influenza. In contrast, many believed that influenza can be prevented by avoiding crowded places (85.1 percent), maintaining good indoor ventilation (81.5 percent), washing hands after sneezing and coughing (75.3 percent), washing hands with liquid soap (74.7 percent), and taking more vitamin C (52 percent). “That explains why most respondents did not get vaccinated,” the spokesman said. “The government should increase public education on the topic.”

The influenza season has arrived earlier than last year in the USA, and the Centers for Disease Control and Prevention (CDC) has warned that infection may reach epidemic proportions. In Hong Kong, increasing influenza activity was reported in January. “We recommend all people in the high-risk group, and anyone who wants to prevent influenza infection, to receive influenza vaccination as soon as possible,” the HA spokesman advised.

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**HA/FSD to improve ambulance services**

Christina Lau

The Hospital Authority (HA) and Fire Services Department (FSD) have agreed to make special arrangements for patients with cardiac or respiratory arrest to be taken to the nearest hospital, following an Ombudsman investigation that found shortfalls in the current system of patient conveyance by ambulance.

Under the current arrangement, Hong Kong is divided into 20 catchment areas, and FSD ambulances are required to take patients to designated hospitals or clinics within the catchment areas (ie, area hospitals) where they are in. This arrangement is based mainly
on the scale, equipment and intake capacity of hospitals. Travel distance, travel time and local traffic conditions are neither the only nor the most important factors for consideration in devising the current plan.

However, a direct investigation reveals that the current practice may lead to delays in patient conveyance.

The Ombudsman reviewed 22 complaint cases received by the FSD over the past 3 years as well as the FSD’s documentary exchanges with the HA. Examples were found, on Hong Kong Island, in Kowloon and the New Territories, in which the area hospital might not be the nearest hospital. “In one case, the travel time to the area hospital was 10 minutes longer than to the nearest hospital,” the report read. “There are concerns that the current fixed rule for ambulancemen to take patients even in critical condition (eg, cardiac arrest or serious respiratory distress) to area hospitals may lead to serious consequences because of delay caused by longer travel time.”

Although the FSD had proposed to adjust the boundaries of catchment areas, agreement was eventually reached with the HA to maintain the existing demarcation on grounds of medical resources and hospital service capacities.

Based on the views of the local medical community and a local patients’ organization, the Ombudsman urged the HA and FSD to make special arrangements so that patients in critical condition are taken to the nearest hospital if the area hospital is not the nearest one.

“We believe that with adequate training and clear guidelines, frontline ambulancemen should be able to identify patients in critical condition and there should not be too much deviation in their assessment,” read the report. “HA statistics showed that, of the patients taken to the Accident and Emergency departments of hospitals by ambulance in the past 3 years, only about 4 percent were identified at the hospital to be in critical condition. We believe that even if all patients in critical condition were taken to the nearest hospitals, that would not have a major impact on the workloads and intake capacities of any particular hospitals.”

The HA and FSD accepted the recommendations, and have agreed to start conveying patients with cardiac or respiratory arrest, who are more identifiable, to the nearest hospital. According to the HA, particular effort would be devoted to providing proper training and facilities as well as drawing up clear guidelines for frontline ambulancemen, including a definition of patients in critical condition.
Hong Kong Events

Symposium on Special Seating, Wheeled Mobility and Advanced Technology – Multidisciplinary Integrated Approach from Hospital to Community
23/2
Department of Orthopedics and Traumatology, CUHK; Department of Orthopedics and Traumatology, AHNH
Tel: (852) 2632 2010
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Annual Scientific Meeting 2013
Hong Kong Thoracic Society and American College of Chest Physicians (Hong Kong and Macau Chapter)
10/3
Info: UBM Medical Pacific Limited
Tel: (852) 2155 8557 / 2116 4348
Fax: (852) 2559 6910
E-mail: meeting.hk@ubm.com

SARS a Decade on: A Conference for the Health Professionals
Stanley Ho Center for Emerging Infectious Diseases, CUHK; Jockey Club School of Public Health and Primary Care, CUHK
12/3
Tel: (852) 2635 4977
Fax: (852) 2252 8819
www.hkcos.org.hk/calendar/

32nd Annual General Meeting cum Scientific Meeting
Hong Kong Society of Gastroenterology
14/3
Tel: (852) 2869 5933
Fax: (852) 2869 9533
E-mail: gastro@hksge.org
http://www.hksge.org/events_news.htm

17th Annual Scientific Meeting
Hong Kong Society of Infectious Disease
16/3
Info: UBM Medica Pacific Limited
Tel: (852) 2155 8557 / 3153 4374
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Correction

In Medical Tribune January 2013, “Linagliptin: Raising expectations in diabetes therapy”:

- Under “Linagliptin in diabetic nephropathy”, last sentence, the correct reference is [ADA 2012; abstract 953-P].

- Under “Long-term use of linagliptin”, the relevant text should read: “The study evaluated subjects who participated in one of four preceding 24-week, randomized, parent trials and who received linagliptin, linagliptin plus metformin, linagliptin plus metformin plus a sulfonylurea or linagliptin plus pioglitazone. **Serious adverse events were reported in 9.9 percent of subjects, with eight deaths occurring over the 78-week extension period; none were considered by the investigator to be related to study drug**.”

The Editor

Industry

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Improving COPD management: GOLD updates in practice .................. P42
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Ticagrelor recommended for STEMI in latest ACC/AHA guidelines

Rajesh Kumar

The American College of Cardiology (ACC) and the American Heart Association (AHA) have updated their clinical practice guidelines for the management of ST-elevation myocardial infarction (STEMI) to include a class I recommendation for the use oral antiplatelet medicine ticagrelor (Brilinta®, AstraZeneca).

The guidelines recommend that reperfusion therapy be given in a timely manner to all eligible patients with STEMI undergoing either percutaneous coronary intervention (PCI) or fibrinolytic therapy. [J Am Coll Cardiol 2012; doi:10.1016/j.jacc.2012.11.019] They also suggest that patients who present to a non-PCI-capable hospital should be considered for transfer either for primary PCI, or if anticipated time to PCI is greater than 2 hours, after fibrinolysis.

Appropriate antithrombotic therapy, including dual antiplatelet and anticoagulant therapy (with clopidogrel, prasugrel or ticagrelor), should be used during and after reperfusion therapy, a report on the guideline revisions added.

The recommendation on “Antiplatelet Therapy to Support Primary PCI for STEMI” (4.4.1) suggested that aspirin at a dose of 162 to 325 mg should be given before primary PCI and should be continued indefinitely thereafter; while a loading dose of a P2Y12 receptor inhibitor such as clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg should be given as early as possible or at the time of primary PCI.

Thereafter, maintenance doses of clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice-a-day should be given for 1 year to those receiving a bare metal or drug-eluting stent during primary PCI.
Vorapaxar after myocardial infarction

The Thrombus Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events (TRA 2° P) – TIMI 50 trial reported in April 2012 showed that treatment with vorapaxar, a selective antagonist of protease-activated receptor 1, for patients with previous myocardial infarction (MI), ischemic stroke or peripheral arterial disease, reduced the risk of cardiovascular death, MI or stroke by 13 percent, but increased the risk of bleeding. Now a subgroup analysis from that trial has concentrated on patients with prior MI. [Lancet 2012;380:1317–1324]

In this subgroup, a total of 17,779 patients had experienced an MI 2 weeks to 12 months previously. Randomization was to vorapaxar 2.5 mg daily or placebo in addition to aspirin, and average follow-up was 2.5 years. Cardiovascular death, MI or stroke occurred in 610 vorapaxar recipients vs 750 patients receiving placebo, giving estimated 3-year rates of 8.1 vs 9.7 percent, a significant 20 percent reduction with vorapaxar. The estimated 3-year rates of moderate or severe bleeding were 3.4 vs 2.1 percent, a significant 61 percent increase with vorapaxar. There was a nonsignificant increase in intracranial hemorrhage with vorapaxar.

The researchers concluded that vorapaxar reduced the risk of cardiovascular death, repeat MI and stroke in post-MI patients, but increased the risk of moderate or severe bleeding.

New mucus-inhibiting therapies may help patients with asthma, COPD

Radha Chitale

New research describing the mucus-causing pathway activated in many respiratory diseases led researchers to develop a series of drugs to inhibit excess mucus production and potentially limit death from these conditions.

“[Excess mucus secretion] is an invariable feature of acute respiratory illness and a characteristic feature of chronic lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD),” said Dr. Michael J. Holtzman, professor of medicine at Washington University School of Medicine in St. Lou-

Lab research points to the potential benefits of therapeutics which inhibit excess mucous production.
is, Missouri, US. “It’s a huge unmet medical problem and is only increasing... throughout the world.”

Stimulants such as allergens, viruses and cigarette smoking activate a pathway that results in extra mucus production, meant to catch small particles and infectious bacteria and keep them from penetrating into respiratory pathways.

Two key players in this pathway are the CLCA1 gene that activates an eponymous protein in response to environmental stimuli. This protein, with help from an enzyme called MAPK13, enables mucus production. [J Clin Invest 2012; doi:10.1172/JCI64896]

Holtzman noted the existence of inhibitors for MAPK14, which is similar to MAPK13.

“These drugs bind to a specific pocket in MAPK14 to block its activity,” he said.

Modifying these therapeutic molecules to make them smaller and a better fit for the inhibiting pockets of MAPK13 resulted in a 100-fold reduction in mucus production in human airway cell cultures.

“These properties should translate into more sustained and potent effects for use as tool compounds and for further drug development,” the researchers said. “Additional work will have to be done to fully characterize the... specificity of the present compounds and perhaps to develop others with greater specificity.”

Importantly, the study was carried out in human cells rather than in a mouse model because of divergent mucus secretion pathways.

Currently, there are few effective treatments for excess mucus, despite mucus overproduction likely being responsible for much of the morbidity and mortality associated with respiratory conditions, the researchers noted.

New MAPK13 inhibitor therapies could impact other conditions in which excess mucus represents respiratory problems, including cystic fibrosis and the common cold.

Having characterized the dominant mucus-causing pathway in people with respiratory diseases, the researchers said “the [study] results validated a novel therapeutic approach to hypersecretory diseases of the pulmonary airways and perhaps other sites as well.”
The US Food and Drug Administration (FDA) has approved bedaquiline for use in combination therapy for adult patients with pulmonary multi-drug resistant (MDR) tuberculosis (TB).

Bedaquiline, the first anti-TB drug to receive US FDA approval in decades following a fast-track review in December 2012, will be marketed under the name Sirturo™ by Janssen Therapeutics.

“New drugs for TB are always welcome, as we haven’t had one in decades,” said Professor Sonny Wang, director of Singapore’s Tuberculosis Control Unit. “There are some uncertainties about side effects around this drug, but the situation in MDR TB is desperate and an additional option for the patients with MDR TB, especially those with high-grade resistance, may be life-saving.”

People with MDR TB are infected with Mycobacterium tuberculosis that has developed resistance to standard first-line drugs such as isoniazid and rifampicin.

The FDA approved bedaquiline following a fast-track review of two phase II trials, one of which is still ongoing, which demonstrated that patients receiving bedaquiline plus existing TB drugs are able to clear infectious bacteria from their sputum faster and better compared with a regimen of existing TB drugs alone. In the completed trial, bedaquiline combination therapy cleared infectious bacteria in a median 83 days compared with 125 days in the control group. The second trial has supporting results so far.

However, in addition to nausea, joint pain and other common side effects, patients receiving bedaquiline in clinical trials were more likely to experience abnormal electrical activity. There were nine deaths reported in patients who took bedaquiline and two deaths among patients on placebo.

Sirturo includes a Boxed Warning for patients and physicians about the side effects and deaths associated with the drug.

“The accelerated approval of Sirturo™ is a significant step in the fight against MDR TB, which is a more difficult to treat form of TB... [which] is on the rise in many areas worldwide,” said Dr. Paul Stoffels, Chief Scientific Officer and Worldwide Chairman of Pharmaceuticals for Johnson & Johnson, Janssen’s parent company.

Out of about 9 million TB cases globally, about 630,000 resist treatment and 440,000 people with drug-resistant TB die each year, according to the WHO Global Tuberculosis Report 2012.

“MDR TB poses a serious health threat throughout the world, and Sirturo provides much-needed treatment for patients who have don’t have other therapeutic options available,” said Dr. Edward Cox, director of the Office of Antimicrobial Products in the FDA’s Center for Drug Evaluation and Research. “However, because the drug also carries some significant risks, doctors should make sure they use it appropriately and only in patients who don’t have other treatment options.”
Individualizing asthma treatment: When to step up or step down?

Jasmine Teo

The variability of asthma between individual patients provides a strong rationale for the routine use of step up/step down therapy in asthma management, an expert says.

“Stepping up and stepping down asthma treatment is a necessary part of asthma management,” surmised Dr. Peter Gibson, senior staff specialist physician, Department of Respiratory and Sleep Medicine, John Hunter Hospital, New South Wales, Australia. “It allows the doctor to provide optimal drug dosing for disease control while minimizing drug exposure and the potential for adverse effects.”

Gibson listed four different approaches to stepping up/down therapy: (1) step up/down based on asthma control assessments, eg, Global Initiative for Asthma (GINA) guidelines; (2) step up/down based on asthma control measures used in combination with inflammatory markers, eg, inflammometry based on fraction of exhaled nitric oxide (FeNO) or induced sputum; (3) variable dosing based on patient perceived symptom recognition; and (4) step up/down based on recognition of a particular phenotype.

The first approach forms the basis of GINA guidelines and relies on an assessment of asthma control linked to a drug dose or class adjustment. The available assessment methods include asthma control questionnaire (ACQ), the asthma control test (ACT), and measures of symptom frequency. Each assessment method has been shown to produce good results – the benefits achieved with this approach are a significant reduction in asthma exacerbations and an increased likelihood of achieving symptom control.

The second approach, which involves the use of inflammometry, has been shown to reduce episodes of severe asthma exacerbations by up to half compared with guideline-based therapy. Sputum eosinophilia serves as a marker of the corticosteroid responsive component of asthma. When it is present, it indicates that the patient requires a higher dosage of corticosteroid.

Customizing doses based on perceived asthma symptom frequency is also a highly efficacious approach leading to a reduced exacerbation frequency. With this approach, patients themselves can adjust their dose of inhaled corticosteroid/long-acting beta-agonist (ICS-LABA).

Finally, step up/down using phenotype-based therapy, whereby the recognition of a particular phenotype leads to improved selection of appropriate drug class and dosage level for the patient. However, Gibson added that presently there are limited data to support this approach.
COPD trials excluding the majority of would-be patient types

Radha Chitale

Healthcare practitioners should carefully gauge the suitability of data from clinical trials involving patients with chronic obstructive pulmonary disease (COPD), says one expert.

Translating clinical trial results into practice can be challenging, said Dr. Christine Jenkins, clinical professor at the Concord Clinical School at the University of Sydney in Australia.

Many patients with COPD are treated based on the results of randomized controlled trials (RCTs) that may not be applicable to them.

In a survey involving 749 adults from New Zealand, 117 were found to have COPD, of whom only 5 percent would have met inclusion criteria for a major COPD treatment RCT as recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. [Respir Med 2007;101:1313-1320]

In other words, over 90 percent of COPD subjects who were taking medication were doing so based on trials for which they would not have been eligible, leading the researchers to suggest that GOLD treatment guideline-based COPD trials have limited external validity.

The same is true of non-pharmacokinetic therapy, Jenkins said, based on the number of patients who dropped out of randomized controlled pulmonary rehabilitation trials – up to 36 percent in intervention groups and up to 54 percent in control groups. [Clin Epidemiol 2010;2:73-83]

“We need to think about how we can include patients who truly represent the patients we look after so we can end up with a population … whom we’re going to give treatment to,” she said.

Because COPD is a heterogeneous disease, correlating changes in lung function as the disease progresses to patient outcomes can be challenging to measure comparatively. Forced expiratory volume (FEV1) can be useful as a static measure of lung function, but Jenkins pointed out that activity functions such as exercise capacity could be more useful for some
patients.

Likewise, COPD exacerbations, although of divergent definition without objective criteria, have long been used to measure outcomes because they are potentially reducible. However, these can also cause patients to drop out of RCTs, reducing the effective trial population.

“Once we only recruit frequent exacerbators, are we excluding a whole population of COPD patients who we actually need to be intervening in and judging whether or not treatment is effective?” Jenkins said.

Some approaches to determining whether patients would benefit from treatments suggested by clinical trials would be to ask if diagnosis was confirmed among the patients in the study as well as the patient in question and whether the patient in question is aligned with the eligibility criteria and demographics of the study population.

Even if the patient would have been excluded from a particular trial, Jenkins pointed out that physicians can still consider the treatment and trial results for the patient, particularly when safety is not an issue.

Examining the characteristics of responders and non-responders to treatment can help to determine if the response would be clinically meaningful in a patient.

Preventing COPD exacerbations requires long-term thinking

Radha Chitale

Managing chronic obstructive pulmonary disease (COPD) means balancing current control with future risk reduction, which is best monitored by examining exacerbation risk and prevention, said Dr. Wisia Wedzicha, professor of Respiratory Medicine at University College London in the UK.

Treating exacerbations early in patients with COPD is critical to reduce the frequency of these escalated respiratory attacks.

“Exacerbation risk is different from exacerbation frequency,” she said. “[Clinicians] must be more proactive; by the time [patients] have become frequent exacerbators, they’ve had it.”

Prompt therapy following symptom onset means patients will recover more rapidly than patients whose therapy gets delayed.

In one study of 108 patients who recorded and reported any COPD exacerbations, earlier treatment led to faster recovery (interquartile range of 7-14 days) than delayed treatment (p<0.001). Failure to report exacerbations was associated with an increased risk of emergency hospitalization (p=0.04).
Am J Respir Crit Care Med 2004;169:1298-1303

“Additionally, patients who do not seek therapy for exacerbations have poorer health-related quality of life and are more likely to be hospitalized for their exacerbations,” Wedzicha said.

A large percentage of exacerbations go unreported. As COPD is a progressive disease, patients with increasingly frequent exacerbations will suffer from increased inflammation, faster disease progression, increased likelihood of hospitalization and increased mortality.

Studies suggest that future exacerbation risk is related to a patient’s exacerbation history. Treatments that reduce exacerbations would be an example of therapy that, beyond providing current control, targets future risk reduction and so is justified. [Prim Care Respir J 2011;20:205-209]

Improving consistent lung function is a part of long-term risk reduction.

In a trial comparing daily peak expiratory flow among 308 COPD patients treated with the long-term anticholinergic tiotropium or a placebo, those given tiotropium showed a consistent pattern of daily peak expiratory flow compared with the random pattern of those on placebo. Random lung function was positively associated with exacerbation frequency per year (p=0.009). [Eur Respir J 2012;40:1123-1129]

Wedzicha said the tiotropium must be changing the property of the airways with prospective day-to-day variation to produce the consistent effect, given that those with random lung function – who were also sometimes the more infrequent exacerbators – were also more susceptible to exacerbations.

“We can prevent exacerbations in different ways if we think about the time course of exacerbation recovery,” she said. “Exacerbations are absolutely key in the balance between current control and future risk reduction.”

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**Novel oral therapies need for treating patients with asthma**

Jasmine Teo

There is a definite need for the development of more oral therapies for asthma, especially for patients with severe forms of the disease in whom current corticosteroid and inhaled medications are ineffective, says an expert from the UK.

Professor Peter Barnes of the National Health and Lung Institute in the UK, said: “It would be desirable to develop an oral therapy that is as effective as combination

The ideal oral asthma therapy would be administered once-daily without side effects.
inhalers,” said Professor Peter Barnes of the National Health and Lung Institute in the UK. While Barnes admitted such treatments might cause problematic side effects, he suggested they may have certain benefits insofar as they might encourage greater patient compliance and they may also help to treat concomitant allergic disease.

Barnes outlined what he considered to be an ideal drug for the treatment of asthma. He said this would be an orally administered agent that can be given once-daily (to help improve patient compliance). It should have no side effects and therapy should be individualized from patient to patient depending on their asthma condition, with the help of pharmacogenomics and identification of specific biomarkers of responsiveness.

However, Barnes conceded that the path to developing new asthma therapies was difficult. Most new treatments have been ineffective or cause side effects, he said.

New diagnostic tools, better treatments needed for TB

Jasmine Teo

Currently available immunodiagnostic tests as well as widely used treatments for tuberculosis (TB) are not particularly effective, according to a new study.

“With the huge problem scale and the number of persons to be treated to prevent one case of TB, further research efforts are required in the development of new diagnostic tools with better disease-predicting ability, as well as shorter and safer regimens, preferably applicable to latent infection by both drug-sensitive and drug-resistant TB,” said study investigator Dr. Chi-Chiu Leung, consultant chest physician with the Tuberculosis and Chest Service, Department of Health, Hong Kong.

Leung and colleagues have reported the results of a meta-analysis of data from 15 studies involving a total of 26,680 subjects in low- and middle-income countries.
Amongst their findings, evidence that commonly used TB diagnostic tools such as interferon-gamma release assay (IGRA) and tuberculin skin test (TST) were not able to identify or predict the development of TB in subjects latently infected with live *Mycobacterium tuberculosis* without active disease.

The research further found that the effectiveness of widely used TB treatments is often limited in real-life settings or in different patient subtypes.

In evaluating patterns of use of several isoniazid-based therapies in patients with latent TB infection, there appeared to be little consistency in terms of optimal duration of treatment, and field efficacies appear to have often been compromised by hepatotoxicity as well as suboptimal patient acceptance and adherence.

Randomized controlled trials of isoniazid therapy have demonstrated efficacy rates of up to 90 percent (for 12 months) of compliance. Prolonged isoniazid therapy among HIV-infected individuals remains controversial with conflicting results in two published trials [*Lancet* 2011;377:1588-98; *N Engl J Med* 2011;365:11-20], whereas it has been proven to be not useful among the non-HIV-infected individuals. Primary isoniazid prophylaxis has also been found to be non-effective among HIV-infected and non-HIV-infected children immunized with BCG vaccine. [*N Engl J Med* 2011;365:21-31] There is also no clear evidence to support the use of chemoprophylaxis for TB patients previously treated and subsequently put on immunosuppressive therapy.

The study also looked at the use of other types of anti-TB regimens, such as those using isoniazid in combination with other medications and non-isoniazid-based regimens, and found these to offer varying degrees of effectiveness and tolerability in preventing or treating latent TB infection.

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Ticagrelor: Latest recommendations underline antiplatelet agent’s usefulness in ACS

Oral antiplatelet agent ticagrelor (Brilinta®, AstraZeneca) was recently given a class I recommendation in the latest revision of the American College of Cardiology (ACC) and American Heart Association (AHA) clinical practice guidelines for the management of patients with ST-elevation myocardial infarction (STEMI). The following article discusses the management of STEMI and other acute coronary syndromes (ACS), profiling the drug ticagrelor.

Naomi Adam, MSc (Med), Category 1 Accredited Education Provider (Royal Australian College of General Practitioners)

Antiplatelet agents for the management of ACS

Cardiovascular diseases remain the leading cause of mortality worldwide and more than half of these deaths involve coronary artery disease with acute coronary syndromes (ACS). Variants include ACS with and without ST-segment elevation, such as unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). [Postgrad Med J 2012;88:391-396]

The pathophysiology of all of these syndromes features the disruption of an atherosclerotic plaque that results in intracoronary thrombogenesis. Platelets play a key role in both the development of atherosclerosis and subsequent thrombosis. In acute thrombosis there is a multiple-step mechanism that involves platelet adhesion, activation and aggregation at the site of injury, followed by cross-linking through fibrin, ultimately leading to obstruction of the coronary vessel. Hence medications that inhibit platelet action are a mainstay of therapy in this setting. [Curr Cardiol Rep 2012;14:457-467]

Aspirin has been the cornerstone of ACS treatment for decades. Its action is mostly due to inactivation of platelet cyclooxygenase 1, which leads to the inhibition of thromboxane generation, and thus disrupts platelet aggregation. However, aspirin alone fails to prevent the majority of recurrent events and this has prompted investigations into alternative methods of blocking platelet action. [Postgrad Med J 2012;88:391-396]

At a molecular level, one of the critical components for platelet aggregation is the platelet P2Y12 receptor. Therefore, blockade of the P2Y12 receptor is an important treatment strategy that is employed in conjunction with aspirin. The clinical benefits of dual antiplatelet treatment with aspirin plus clopidogrel in
the management of ACS are well established. However, clopidogrel is a pro-drug that requires hepatic activation and there are several concerns regarding its use. These include delayed onset of action, variability in antiplatelet effects, prolonged recovery of platelet function after discontinuation and interactions with commonly used agents such as proton pump inhibitors. While the use of clopidogrel has been a beneficial advance in the treatment of ACS, its shortcomings have prompted investigations of alternative P2Y12 receptor antagonists. [Postgrad Med J 2012;88:391-396, Curr Cardiol Rep 2012;14:457-467]

Ticagrelor
Ticagrelor is the first member of a new class of antiplatelet agents – the cyclopentyltriazolopyrimidines – to undergo clinical development. Its inhibitory effects on platelet function are mediated predominantly via the P2Y12 receptor, however, ticagrelor provides more effective inhibition of platelet function, with a faster onset and offset of action than clopidogrel. [Drugs 2011;71:909-933]

Pharmacokinetics and metabolism
Following oral administration, ticagrelor is rapidly absorbed and converted to its major metabolite – AR-C124910XX. Unlike clopidogrel, ticagrelor is itself an antagonist of the P2Y12 receptor. The pharmacokinetics of ticagrelor are linear with dose-proportional exposure up to doses of 1,260 mg. Peak plasma concentrations are reached at a median of 1.5 hours of administration and it has a mean half-life of 7 hours. The timing of a meal relative to a dose of ticagrelor has no appreciable effect upon its pharmacokinetics. [Drugs 2011;71:909-933]

Metabolism of ticagrelor occurs predominantly via CYP3A4 and CYP3A5. Elimination of ticagrelor and AR-C124910XX occurs primarily via hepatic metabolism and biliary secretion, respectively. [Drugs 2011;71:909-933]

Clinical efficacy
The pivotal clinical trial of ticagrelor was the Platelet Inhibition and Patient Outcomes (PLATO) study. This was a multicenter, double-blind, randomized trial that compared P2Y12 antagonists for the prevention of cardiovascular events on a background of aspirin therapy in 18,624 patients hospitalised with an ACS. Subjects were assigned to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300–600 mg loading dose, 75 mg daily thereafter). The primary efficacy endpoint was the time to the first occurrence of composite of death from vascular causes, myocardial infarction, or stroke. After 12 months of follow up, the primary endpoint occurred significantly less often in the ticagrelor group than in the clopidogrel group (in 9.8 percent of patients vs 11.7 percent; hazard ratio, 0.84; 95% CI 0.77–0.92; p<0.001). There was no difference in the overall major bleeding rate between the two groups, though ticagrelor was associated with a significant increase in the rate of non-procedure-related bleeding. [N Engl J Med 2009;361:1045-1057]

Adverse effects
In clinical trials, adverse events associated with ticagrelor included ventricular pauses, dyspnea, hyperuricemia, and increased creatinine. [Drugs 2011;71:909-933] Contraindications according to the product label are active pathological bleeding, a history of intracranial hemorrhage and moderate-to-severe hepatic impairment. The label also states that ticagre-
lor should be used with caution in patients at risk of bleeding (e.g., recent trauma, surgery, GI bleeding, concomitant NSAIDs or fibrinolytics). If a patient reports new, prolonged or worsened dyspnea, this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped. [Brilinta Product Monograph. February 2012]

There is a potential for drug interactions mediated by CYP3A4, hence co-administration with strong inhibitors such as ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir is contraindicated. [Drugs 2011;71:909-933, Brilinta Product Monograph. February 2012]

**Dosing**

The approved dosage is as per that used in the PLATO trial: treatment should be initiated with a loading dose of 180 mg ticagrelor (two tablets of 90 mg) and then continued at 90 mg twice a day for up to 12 months. Patients taking ticagrelor should also take low-dose aspirin daily, unless specifically contraindicated. Following an initial loading dose of aspirin, the maintenance dose is 75–150 mg per day.

**Guideline recommendations for ticagrelor**

The UK National Institute for Clinical Excellence has recommended that ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults ACS, including those with:

- ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI)
- non-ST-segment-elevation myocardial infarction (NSTEMI) or admitted to hospital with unstable angina – defined as ST or T wave changes on electrocardiogram suggestive of ischemia.

The NICE recommendations further suggest that before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist. [NICE technology appraisal guidance 236. www.nice.org.uk/ta236. October 2011]

Subsequently, the American Heart Association (AHA) Task Force on Practice Guidelines and the American College of Cardiology Foundation (ACCF) have also updated their recommendation to state that ticagrelor should be considered as an equal option to clopidogrel for patients with NSTEMI [Circulation 2012; 126: 875–910] and for STEMI [J Am Coll Cardiol 2012; doi:10.1016/j.jacc.2012.11.019].

Further long-term and comparative efficacy and tolerability data will be needed to definitively position ticagrelor with respect to other antiplatelet agents. However, the data so far indicate that ticagrelor is a promising option for the treatment of patients with ACS and may be of particular use in those at high risk of ischemic events or unresponsive to clopidogrel.

**Author disclosures:** None
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PASSION FOR INNOVATION
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How long attempts to resuscitate patients after cardiac arrest should continue is uncertain. A study at 435 US hospitals has provided useful information.

Between 2000 and 2008, there were 64,339 patients with cardiac arrest at the 435 hospitals; 31,198 patients (48.5 percent) had return of spontaneous circulation after resuscitation and 9,912 (15.4 percent) survived to hospital discharge. Among non-survivors, the median duration of resuscitation was 20 minutes. Return of spontaneous circulation and survival to hospital discharge were each 12 percent more likely in hospitals in which average resuscitation time for non-survivors was longer (25 minutes) compared with those in which it was shorter (16 minutes).

Hospitals in which resuscitation attempts were longer in non-survivors had better rates of return of circulation and survival.

Job strain and coronary disease

There is evidence that job strain (high job demands and low job control) may increase the risk of coronary disease. Present evidence, however, is possibly subject to publication bias and there may be an element of reverse causation. Now a meta-analysis of published and unpublished studies has suggested a small but significant effect of job strain.

The meta-analysis included individual participant data from 13 European cohort studies (197,473 participants with no coronary disease at baseline from 1985 to 2006). Job strain was measured by questionnaire. Incident coronary disease was defined as coronary death or first nonfatal myocardial infarction. Job strain was reported by 15 percent of participants. Over a mean follow-up of 7.5 years, there were 2,358 incident coronary disease events. After adjustment for age and sex, job strain was associated with a significant 23 percent increase in risk of incident coronary disease (43 percent in published studies, 16 percent in unpublished). After exclusion of coronary events occurring within 5 years of baseline, the increase associated with job strain was 30 percent. The association of coronary disease with job strain remained significant after adjusting for multiple confounding factors. The population attributable risk was 3.4 percent.

It is concluded that job strain increases coronary risk but the effect is small compared with standard risk factors such as smoking.

People who self-harm are at increased risk of death from suicide, accidents, and natural causes. Both self-harm and suicide are associated with low socioeconomic status. Now a study based on emergency departments in three English cities (Oxford, Manchester and Derby) has shown that people who self-harm often have physical as well as psychological problems and their life expectancy is compromised.

The study included 30,950 people who presented to the three emergency departments with self-harm (self-poisoning or self-injury) in the years 2000 to 2007. The average follow-up was for 6 years and overall mortality during follow-up was 6.1 percent. The standardized mortality rate was 3.6 (4.1 for males and 3.2 for females). Deaths from natural causes were up to 7.5 times more frequent than expected. All-cause deaths meant 31 years of life lost (YLL) for both males and females who self-harmed. For deaths from natural causes the YLL was around 26 years, and for deaths from external causes 40 years. Circulatory system deaths accounted for 13 percent of deaths and digestive system deaths for 12 percent of male deaths and 18 percent of female deaths. All-cause mortality was strongly related to socioeconomic deprivation in both sexes. Socioeconomic deprivation was associated with an increased risk of death from natural causes but not from external causes.

Self-harm is associated with both physical and mental health problems and with many years of life lost.

Dengue vaccine in Thailand

It is thought that about half of the global population are at risk of contracting dengue. There is no specific treatment and no vaccine. Now a recombinant, live, attenuated tetravalent dengue vaccine (CYD-TDV) has been assessed in Thailand.

A total of 4,002 schoolchildren aged 4–11 years were randomized (2:1) to dengue vaccine or control (rabies vaccine or placebo) with three doses at 6-month intervals, and followed up for 25 months. The vaccine efficacy against virologically confirmed symptomatic dengue occurring at least 12 months after the third dose was 30.2 percent. This low overall efficacy was explained by a very low (not significantly different from zero) efficacy against serotype 2 virus, which caused 59 percent of the dengue episodes. Efficacy against serotypes 1, 3 and 4 was 61 percent, 82 percent and 90 percent, respectively. The vaccine was well tolerated.

The vaccine is safe and effective against three of four serotypes. Further studies are planned.


Benzodiazepines and dementia risk

Case-control and cohort studies have shown that benzodiazepines may affect cognition. A study in France has shown that benzodiazepine use is associated with an increased risk of dementia.

The PAQUID study was a 20-year follow-up study of a cohort of 3,777 unselected people aged 65 or over in southwest France. An analysis of a main cohort of 95 new users of benzodiazepines and 968 non-users (mean age, 78 years) showed a significant increase in risk of dementia of 62 percent associated with new use. Pooled analysis of five cohorts showed a significant 43 percent increase in risk. A nested case-control analysis including 467 patients with dementia and 1,810 controls showed a 55 percent increase in risk with ever-use compared with never-use. The risk was increased significantly only in past users (at least 5 years previously) and not in recent users. Adjustment for factors associated with benzodiazepine use and for factors possibly predictive of dementia did not alter the findings.

Benzodiazepine use in the past is associated with increased risk of dementia.

Resistance to second-line drugs in MDR tuberculosis

The emergence of extensively drug-resistant (XDR) tuberculosis and its increasing prevalence are consequences of the increased use of second-line drugs for multidrug-resistant (MDR) tuberculosis. A study in eight countries (Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand) has illustrated the problem.

The study included 1,278 consecutive adults with MDR tuberculosis during the years 2005 to 2008. Overall, 43.7 percent of these patients showed resistance to at least one second-line drug, 20.0 percent to at least one injectable second-line drug, and 12.9 percent to at least one fluoroquinolone. The prevalence of XDR tuberculosis was 6.7 percent (varying from 0.8 percent in the Philippines to 15.2 percent in South Korea). The strongest risk factor for resistance to second-line drugs was previous treatment with these drugs and this increased the risk of XDR tuberculosis more than fourfold. Resistance to second-line drugs was also associated with unemployment, alcohol abuse and smoking. Fluoroquinolone resistance and XDR tuberculosis were more prevalent among women than among men.

Previous treatment with second-line drugs is the strongest risk factor for resistance to these drugs and XDR tuberculosis. Policies for laboratory capacity and diagnostic strategies could be guided by representative drug-susceptibility information in each country.

Opiate substitution reduces HIV risk

Opiate substitution treatment is used for addiction to heroin or other opioids and associated reductions in injecting risk behavior may reduce the risk of HIV infection. A systematic review and meta-analysis has confirmed this protection.

The review included 12 published and three unpublished studies of methadone maintenance treatment with over 26,738 person-years of follow-up and 1,016 new HIV infections. A meta-analysis of nine studies showed that opiate substitution treatment was associated with a significant 54 percent reduction in HIV risk among people who inject drugs. There was a suggestion that the risk reduction might increase with duration of opiate substitution treatment. Geographical region, the provision of incentives, site of recruitment, and the proportion of subjects who were women or from ethnic minorities did not affect the findings.

Opiate substitution therapy significantly reduces the risk of HIV infection among people who inject drugs.

Improving COPD management: GOLD updates in practice

Chronic obstructive pulmonary disease (COPD) exacerbations have a negative impact on quality of life (QoL) and are a common cause of mortality. The revised Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 strategy document was published with the aim to improve the assessment and management of COPD. The new document recommends the use of long-acting beta-2 agonist/inhaled corticosteroid (LABA/ICS) combinations such as salmeterol/fluticasone (Seretide®, GSK) as maintenance therapy in newly-diagnosed COPD patients. At a GSK-sponsored symposium during the 17th Congress of the Asia Pacific Society of Respirology in Hong Kong, Professor Wisia Wedzicha of the University College London and the Royal Free Hospital, London, UK, discussed important aspects of COPD management with reference to the GOLD updates.

GOLD 2011 updates

“The large variation between lung function and health status in COPD patients was the impetus behind framing the new multidimensional assessment strategy for COPD,” said Wedzicha.

According to the revised GOLD recommendations, COPD patients are now stratified into categories A, B, C and D based on symptoms, level of lung function, and history of exacerbations. In the earlier version (2006), classification of severity was based mainly on levels of forced expiratory volume in 1 second (FEV1). FEV1 alone is an unreliable marker of breathlessness severity, exercise limitation, and health status impairment. In the new classification, the two symptom cut-off points proposed are COPD Assessment Test (CAT) score ≥10 and Modified Medical Research Council Dyspnea (mMRC) grade ≥2. [GOLD 2011; http://www.goldcopd.org] “The mMRC cut-off point of ≥2 appears to shift a substantial proportion of patients to the low-symptom quadrants. Future modification of the group cut-off points with respect to mMRC scores may be required,” remarked Wedzicha.

The 2011 classification identifies a higher number of individuals at risk of exacerbations, thus providing a better prognostic separation. [Am J Respir Crit Care Med 2012;186:975-981]

Pharmacotherapy options

Initiating maintenance treatment at early stages of COPD significantly improves patients’ long-term health and QoL. [Prim Care Respir J 2011;20:33-45] According to the new recommendations, disease staging (A, B, C or D) influences the choice of therapy.

For patients with stable COPD, the first choice is short-acting beta-agonists or short-acting anticholinergics for category A disease, and LABA, or long-acting muscarinic antagonist (LAMA), or both for category B disease. The importance of LABA + LAMA therapy, which improves lung function and hyperinflation more than either drug alone, has now been recognized. “For patients with stable category C or D disease, the first choice is a LABA/ICS combination,” remarked Wedzicha.

The revised document does not recommend use of ICS unless it is in combination with a LABA. Inhaled LABA/ICS combinations with a
LABA. Inhaled LABA/ICS combinations may be used in patients with more severe airflow limitation (FEV1 <50 percent predicted) and/or a history of frequent exacerbations. [http://www.goldcopd.org/uploads/users/files/GOLD_AtAGlance_2011_Jan18.pdf]

Implications of frequent exacerbations

“Frequent exacerbations drive disease progression,” said Wedzicha. According to GOLD 2011, an exacerbation of COPD is “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.” Exacerbations accelerate lung function decline, resulting in reduced physical activity, poorer QoL, and an increased risk of death. [N Engl J Med 2010;363:1128-1138] A recent study showed that differences in exacerbation rates for patients in the highest risk category D were seen depending on whether risk was based on lung function, exacerbation history, or both. [Lancet Resp Med 2012, e-pub 1 Sep; doi:10.1016/S2213-2600(12)70044-9] Exacerbations increase the risk of MI and stroke, which may have implications for therapy in both stable and exacerbated COPD. [Chest 2010;137:1091-1097]

The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study (n=2,138) showed that exacerbations became more frequent and more severe as the severity of COPD increased. “A history of hospitalization considerably reduces survival,” said Wedzicha. The most important determinant of frequent exacerbations is a history of exacerbations. Exacerbations are therefore likely to predict treatment. History of frequent exacerbations (≥2 exacerbations in the previous year) is a strong predictor of future risk. (Figure 1) [N Engl J Med 2010;363:1128-1138; Prim Care Respir J 2012;21:437-441]

Maintaining active treatment with LABA/ICS combo

Maintaining active treatment with a LABA/ICS combination is beneficial for COPD control, as a trial demonstrated disease deterioration after ICS withdrawal from a LABA/ICS combination. The trial investigated the effects of 1-year withdrawal of fluticasone propionate (FP) after a 3-month run-in treatment period with FP combined with salmeterol (S). “Deterioration was observed fairly early when FP was withdrawn,” said Wedzicha. Withdrawal of FP resulted in persistent deterioration in lung function, increase in mild exacerbations, dyspnea and percentage of disturbed nights, and a decrease in the percentage of rescue medication-free days. (Figures 2 and 3) “The risk of withdrawal is higher in patients with FEV1 < 50 percent predicted,” said Wedzicha. [Thorax 2005;60:480-487]

These results are similar to the earlier COPE study, showing that FP discontinuation is associated with a more rapid onset and higher risk of recurrent exacerbations, and a significant deterioration in aspects of health-related QoL (ie, symptom, activity, impact). [Am J Respir Crit Care Med 2002;166:1358-1363]

Detection and assessment of exacerbations

Exacerbation frequency is an important determinant of decline in lung function in COPD. [Thorax 2002;57:847-852] “A significant number of exacerbations are not reported,” said Wedzicha.

Detection and measurement of exacerbations improve the understanding of the disease and its treatment by reducing random
error and misclassification bias. The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a patient-reported outcome (PRO) measure designed to provide a single, standardized, reliable and valid method for assessing frequency, severity and duration of COPD exacerbations. It is a 14-item diary assessing breathlessness, cough and sputum, and chest symptoms designed to quantify exacerbation outcomes in COPD. [Am J Respir Crit Care Med 2011;183:323-329]

An observational study showed that EXACT scores are internally consistent and reproducible, valid, and sensitive to changes that occur during recovery from exacerbation. [Am J Respir Crit Care Med 2011;183:323-329] “The EXACT-PRO is the instrument of choice for acute exacerbation studies,” said Wedzicha. “Frequent exacerbators need to be recognized and prioritized for therapy.”

![Figure 1. Exacerbation history: Powerful predictor of exacerbations](image)

![Figure 2. Withdrawal of ICS from LABA/ICS significantly increases exacerbation rate](image)

![Figure 3. Withdrawal of fluticasone from SFC](image)
Impact of early-life nutrition on NCD development in adulthood

The risk of developing some chronic non-communicable diseases (NCDs) in adulthood is influenced not only by genetic and lifestyle factors, but also by environmental processes that operate in the periconceptual, fetal and infant phases of life. At a Danone-sponsored symposium held recently in Hong Kong, Professor Sir Peter Gluckman of the Liggins Institute, University of Auckland, New Zealand discussed the evidence linking early-life conditions (e.g., nutrition) with later-life outcomes and the opportunities it presents for controlling the global epidemic of NCDs such as obesity and diabetes.

NCD etiology: Not simply about adult lifestyle

“Until recently, discussion about obesity and chronic NCDs has been dominated by a focus on ‘voluntary’ adult lifestyle factors. However, this model is not working well because the rate of obesity and the prevalence of NCDs have continued to rise,” said Gluckman. “Progress in developmental sciences tells us that there are more fundamental drivers underlying the development of NCDs.”

As Gluckman pointed out, the issue is fundamentally an evolutionary mismatch between our current patterns of nutrition and energy expenditure and those when the human species evolved. “Obesity and diabetes are problems of evolutionary mismatch. Our current patterns of nutrition and energy expenditure have exceeded what our metabolic system can cope with,” he suggested.

“Although most of us now live in a world of excess nutrition, there are major individual and population differences in our vulnerability to adiposity and diabetes,” he noted.

For example, a multi-ethnic cohort study of 59,824 non-diabetic adults aged ≥30 years living in Ontario, Canada showed that for the same body mass index (BMI), Indians had about three times the risk of developing type 2 diabetes compared with Caucasians, while Chinese had double the risk. “The increase in risk is observed not only in the high BMI range, but also in BMIs as low as 20,” said Gluckman. [Diabetes Care 2011;34:1741-1748]


Early-life conditions linked to later-life health

According to Gluckman, there is an incontrovertible body of experimental, clinical and epidemiological evidence linking early-life conditions to later-life health outcomes such as obesity, insulin resistance, type 2 diabetes, cardiovascular disease, osteoporosis, allergy,
mood disorders, some cancers, and longevity. (Figure 1) [Science 2004;305:1733-1736]

“These early-life conditions include health and nutrition of the mother before and during pregnancy, as well as nutrition and growth in the fetal and early postnatal phases of life,” he said. “They determine the structure, function and adaptive capacities of key organs, and define the capability of an individual to interact with the environment.”

As Gluckman explained, the embryo, fetus and neonate constantly take signals from the mother regarding the nutrition and broader environment of the world where it will grow and reproduce. “In general, it uses this information to inform subtle changes in its development so that it physiologically matches the world it will live in. This is a normal process in every pregnancy and involves inheritable epigenetic as well as neurodevelopmental programming,” he said.

The most sensitive window for epigenetic programming is during early development. [Am J Clin Nutr 2011;93(Suppl):897S-900S; Pediatr Res 2007;61:5R-10R; FASEB J 2011;25:1378-1369] Extensive research suggests that exposure to environmental compounds or behaviors, placental insufficiency, maternal nutrition, and metabolic disturbances or disease can promote improper epigenetic programming, leading to susceptibility to various diseases in the first and even subsequent generations. [Br J Nutr 2010;104 (Suppl 1):S1-S25]

Impact of maternal nutrition on offspring’s disease risk

Maternal nutrition during pregnancy may have a long-lasting impact on the offspring’s disease risk.

In a study of rats exposed to a high-fat diet after weaning, those born to mothers undernourished in pregnancy had significantly more retroperitoneal fat than those born to mothers with a normal diet during pregnancy. The former also developed the metabolic syndrome in adulthood. [Am J Physiol 2000;279:E83-E87]

In children, the risk of obesity at 2-4 years of age was more than doubled if mothers were obese during early pregnancy. [Pediatrics 2004;114:e29-e36] Furthermore, a recent study showed that maternal diet during pregnancy affects the epigenetic state of a gene that predicts a child’s later body composition. [Diabetes 2011;60:1528-1534] “By analyzing umbilical cord tissue DNA taken from healthy neonates, researchers found that the epigenetic state of the RXRA gene at birth predicted about 30 percent of variation in body composition 6-9 years later,” said Gluckman. “Any variation in the epigenetic state of DNA at birth means that the in-utero experience was different. Indeed, the researchers found that higher RXRA gene promoter methylation was associated with lower maternal carbohydrate intake in early pregnancy, which was previously linked to higher neonatal adiposity. This association was independent of the mother’s BMI or the offspring’s birth weight.” (Figure 2)

Based on the evidence available, Gluckman emphasized that it is important for pregnant women to manage weight gain, have a balanced intake of macro- and micronutrients, and avoid smoking, drugs or alcohol. “There is considerable evidence on the effects of macro- and micronutrients on gestational length and birth weight,” he said. “For pregnant women, it is also important to screen for pre-existing overt diabetes and gestational diabetes, as children of diabetic mothers have a high risk of developing obesity and diabetes. For those
with pre-existing or gestational diabetes, good glycemic control during pregnancy is crucial.”

It is also important to encourage girls and young women to adopt key health behaviors before conception, as maternal factors during the pre-conception period may affect the child’s later development through epigenetic mechanisms. For example, it has been reported that specific epigenetic settings in the infant at birth were related to the pre-conception diet of the mother. [PLoS Genet 2010;6:e1001252] “Girls and young women should therefore have a balanced diet, adequate physical activity and healthy body weight, so that they are more likely to have a healthy body composition at conception. We should focus on both macro- and micronutrients, and screen for diabetes before conception in women with risk factors,” suggested Gluckman. “Balanced nutrition is equally important for fathers, as there is evidence that epigenetic imprinting may affect the next generation through the paternal lineage.”

**Importance of breastfeeding and appropriate weaning**

The WHO recommends breast milk as the perfect food for newborns. Exclusive breastfeeding is recommended up to 6 months of age, with continued breastfeeding along with appropriate complementary foods up to 2 years of age or beyond. [http://www.who.int/topics/breastfeeding/en/]

“There has been an increasing focus on the role of the gut microbiota in human metabolic and immune health,” said Gluckman. “There are differences in the gut microbiota between breastfed and formula-fed infants, and between those born by vaginal delivery and Caesarean section. Probiotics and pre-biotics may have a role for long-term health.”

In addition to the promotion of breastfeeding, Gluckman stressed that appropriate weaning strategies are crucial as they have a lifelong influence on an individual’s taste and food preference.

**Conclusion**

Nutrition during the periconceptual, fetal and infant phases of life can influence an individual’s risk of developing NCDs such as obesity and diabetes in adulthood. As studies have shown, maternal nutrition before conception may also have a long-lasting impact on the child’s disease risk. The evidence thus calls for a life-course and intergenerational approach of nutritional education starting early in life to control the current NCD epidemic in both developing and developed countries.
Once-daily bronchodilators for better COPD control

Chronic obstructive pulmonary disease (COPD) is projected to become the fourth leading cause of death worldwide by 2030, possibly due to an increase in tobacco smoking and demographic changes in many countries. At the 17th Congress of the Asian Pacific Society of Respirology held recently in Hong Kong, Professor Kai M. Beeh of the Insaf Respiratory Research Institute in Wiesbaden, Germany discussed the role of long-acting bronchodilators in achieving symptomatic control in COPD, with a focus on the use of once-daily indacaterol (Onbrez®, Novartis).

Long-acting bronchodilators: Cornerstone of treatment

“Bronchodilators, in particular long-acting bronchodilators, are the cornerstone of COPD treatment,” said Beeh. “They have demonstrated beneficial effects on a number of important outcomes such as improvements in airflow, hyperinflation and exercise capacity; reduction of dyspnea and prevention of exacerbations.”

Recent therapeutic developments in COPD represent a paradigm shift from short-acting to long-acting bronchodilators with significantly reduced dosing frequency. “The prolonged duration of action of long-acting bronchodilators means patients are able to gain similar, if not better, improvements in lung function over 24 hours than if treated with a short-acting bronchodilator,” said Beeh. “There is good evidence that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.” [Adv Ther 2010;27:150-159]

Indacaterol improves clinical outcomes and health status

Indacaterol is a novel once-daily long-acting beta-2 agonist (LABA) that has demonstrated superior bronchodilation and clinical efficacy over several other twice-daily LABAs and at least equipotent bronchodilation vs once-daily tiotropium. “The INLIGHT-2 [Indacaterol Efficacy Evaluation Using 150 µg Doses with COPD Patients] study was significant as it further confirms the hypothesis that prolonging the duration of bronchodilator action provides added benefit to COPD patients,” Beeh noted.

In INLIGHT-2, a total of 1,002 patients with moderate-to-severe COPD were randomized to 6 months of double-blind treatment with indacaterol 150 µg once daily, salmeterol 50 µg twice daily or placebo. The primary efficacy endpoint was trough forced expiratory volume in 1 second (FEV1) at 12 weeks. [Eur Respir J 2011;37:273-279]

At week 12, patients receiving indacaterol had a higher trough FEV1 than those receiving placebo or salmeterol (170 mL and 60 mL higher, respectively; both p<0.001). Trough FEV1 was significantly greater with indacaterol vs salmeterol at both week 12 and week 26 (by 60 mL and 70 mL, respectively; both p<0.001). (Figure 1) “This difference in lung function was impressive,” said Beeh. “Introducing a once-daily drug enables you not only to reduce dosing frequency, but also to improve the physiological benefit for the patient.” [Eur Respir J 2011;37:273-279]
Another important aspect of INLIGHT-2 was the measurements of health status and dyspnea between patient groups, using the St George's Respiratory Questionnaire [SGRQ] and transition dyspnea index [TDI] scores, respectively,” said Beeh. At week 12, SGRQ and TDI scores were significantly better in the indacaterol group vs the salmeterol group. (Figure 2) The sustained reduction in dyspnea was an important finding for indacaterol as breathlessness is considered the most disabling symptom for COPD patients. [Eur Respir J 2011;37:273-279]

Better patient-reported outcomes
The INTENSITY study was the first blinded study comparing indacaterol with tiotropium, aiming to demonstrate that indacaterol has a similar, and potentially superior, efficacy profile vs tiotropium over 12 weeks of treatment. Involving a total of 1,598 patients with moderate-to-severe COPD, the study showed that indacaterol 150 µg and tiotropium 18 µg had similar overall effects on trough FEV1 (1.44 L and 1.43 L, respectively; p<0.001 for non-inferiority) at 12 weeks. [Eur Respir J 2011; 38:797-803]

“How ever, if you look at patient-reported outcomes, you can see that indacaterol patients were significantly more likely to achieve clinically relevant improvements in TDI and SGRQ scores than tiotropium patients,” Beeh pointed out. (Figure 3) Indacaterol-treated patients also had greater improvements in TDI and SGRQ total scores than tiotropium-treated patients (both p<0.001). [Eur Respir J 2011;38:797-803]

“These results clearly illustrate the disparity between pure physiological outcomes and patient-reported outcomes in COPD,” said Beeh. “In the study, the better patient-reported outcomes with indacaterol could be due to its faster onset of action. This is something that patients favor greatly, as it gives them immediate relief of dyspnea.”

More recently, a pooled analysis from controlled studies presented at the 2012 European Respiratory Society Congress showed that indacaterol 300 µg was superior to open-label tiotropium 18 µg in improving dyspnea in patients with highly symptomatic COPD (p<0.05). [Eur Respir J 2012;40:372s-373s] “This may provide a rationale for increasing indacaterol dosage to 300 µg to achieve further control in patients with severe dyspnea,” Beeh opined.

Preventing exacerbations and improving physical activity
“Exacerbations are very important events in COPD. They can determine a patient’s risk of hospitalization or, in some cases, mortality,” said Beeh. Exacerbations, he noted, can directly affect patients’ physical activity, which is an important prognostic factor in COPD. “Physical activity is, in turn, very closely linked to the concept of hyperinflation in COPD.”

“Hyperinflation is a result of expiratory flow limitation in COPD, which causes increased air trapping in the lungs,” said Beeh. This expiratory flow limitation, he noted, impacts on the time constant for expiration, making it too short to allow for full exhalation. “Over time, hyperinflation leads to a very uncomfortable sensation known as dyspnea, thereby impacting the patients’ daily activities.”

“Long-acting bronchodilators can provide pharmacological reduction of lung volume. This means that the more we reduce the net diameter of the peripheral airway, the more likely the trapped air within the lungs will be released, thereby resulting in a reduction in
hyperinflation,” Beeh explained. In a study comparing the effect of once-daily indacaterol 300 µg vs twice-daily salmeterol 50 µg on inspiratory capacity, indacaterol was associated with significantly higher inspiratory capacity over 24 hours (p<0.05). “This indicates a better reduction in hyperinflation with indacaterol compared with salmeterol, thereby improving the patients’ physical capacity.” [Pulm Pharmacol Ther 2011;24:162-168]

According to Beeh, physical capacity is not the same as physical activity. “Being able to do more does not necessarily mean patients can or will do more.” In a recently published study that tackled this particular issue, investigators assessed the effects of indacaterol 150 µg on lung volume and physical activity vs placebo. At study end, inspiratory capacity was 0.19 L greater in the indacaterol group vs placebo (p<0.001). More importantly, physical activity, as measured by steps per day and minutes of moderate activity per day, significantly improved in the indacaterol-treated group compared with placebo (7,341 vs 6,618 steps per day, p=0.019; 125 vs 97 minutes of moderate activity per day, p=0.017). [Am J Respir Crit Care Med 2012;185:A2257]

**Conclusions**

“Ultimately, the choice of COPD drug should be based on evidence of good clinical efficacy,” said Beeh. Once-daily indacaterol, he concluded, has proven advantages over twice-daily bronchodilators and even once-daily tiotropium in terms of symptomatic improvements or lung function endpoints, and this may be related to its fast onset of action. Long-acting bronchodilators also impact future risk as they can prevent exacerbations and more importantly, increase physical activity in COPD patients. “Eventually, this will result in a reduction in morbidity and mortality, and for me, that is the ultimate goal of COPD therapy.”
Managing age-related macular degeneration

Age-related macular degeneration (ARMD) is the most common cause of irreversible loss of central vision in people beyond the age of 50 in the developed world. [BMJ 2003;326(7387):485-8] Asian studies show that its prevalence in Asians is largely similar. [Invest Ophthalmol Vis Sci 2007;48:1007-11, Ophthalmology 2010;117(5):921-7]

ARMD is a progressive disorder and its diagnosis rests on signs in the macula. Drusen and changes in the retinal pigment epithelium (such as hyper- and hypopigmentation) are the characteristic physical signs of ARMD. [New Engl J Med 2006;355:1474-85]

Classification

In the conventional method, ARMD is classified into two types: dry or non-exudative ARMD, and wet or exudative ARMD. Dry ARMD, which makes up about 90 percent of diagnosed disease, has a more gradual progression. Its advanced stage is characterized by geographic atrophy (GA). Wet or exudative ARMD is associated with rapid progression of disease leading to visual loss. It is characterized by choroidal neovascularization (CNV), which is the abnormal growth of blood vessels (choriocapillaries) in the Bruch membrane, leading to pigment epithelial detachment. [Kanski JJ and Bowling B. Clinical Ophthalmology: A Systematic Approach. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7, New Engl J Med 2006;355:1474-85, Exudative ARMD. Available at: emedicine.medscape.com/article/1226030 Accessed on 5 December, Nonexudative ARMD. Available at: emedicine.medscape.com/article/1223154 Accessed on 5 December]

The IARMESG classification divides ARMD into early ARMD, characterized by medium-large drusen, or by hyperpigmentation and/or small hypopigmentation; and
advanced ARMD, which is more severe, with the presence of either GA or CNV. [Kanski JJ and Bowling B. *Clinical Ophthalmology: A Systematic Approach*. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7] Visual symptoms are inconspicuous in the early stages of ARMD.

Drusen is extracellular yellowish colored material deposited beneath the retinal pigment epithelium (RPE). They become visible on ophthalmoscopy when their diameter exceeds 25 µm. [Br J Ophthalmol 1999; 83:358-68] Drusen can be hard or soft. Although the underlying pathophysiology of hard and soft drusen is similar, from a clinical and histopathological point of view there is a clear distinction. [Kanski JJ and Bowling B. *Clinical Ophthalmology: A Systematic Approach*. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7] Hard drusen, which consist of hyaline material, are well-defined, substantially smaller and are associated with a lower risk of visual loss. Soft drusen (semi-solid deposits) can enlarge and combine to cause elevation of the RPE and loss of vision.

**Risk Factors**

Age is a major risk factor (usually over 65). Other risk factors include gender (women are at higher risk), hereditary, cigarette smoking (which almost doubles the risk), hypertension, diet (high fat intake and obesity) and lack of exercise. [Holz FG, Pauleikhoff D, Spaide RF and Bird AC (2004) *Age-Related Macular Degeneration*. Heidelberg, Germany: Springer-Verlag, Chapter 1: Epidemiology of Age-related Maculopathy. A review (pages 2-15), Kanski JJ and Bowling B. *Clinical Ophthalmology: A Systematic Approach*. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7, Exudative ARMD. Available at: emedicine.medscape.com/article/1226030 Accessed on 5 December] and gaps in an image. [New Engl J Med 2006; 355:1474-85] Peripheral vision is usually retained. Small areas of geographic atrophy do not noticeably compromise good vision. Dry AMD may, therefore, remain unrecognized in its early stages.

Patients with wet ARMD present with a more rapid onset of painless blurring of central vision. They may complain of metamorphopsia (image distortion) and central scotoma (partial loss of vision or a blind spot in an

Fluorescein angiography (FA), a method for examining the intraocular vascular beds, is used to confirm a diagnosis of CNV. Indocyanine green angiography (ICGA) uses an intravenous dye with different characteristics from FA (eg, less melanin absorbance) and it has an increased sensitivity in the detection of CNV. Optical coherence tomography (OCT), a newer optical imaging method, is now widely used for early diagnosis and progression of CNV and patient’s response to therapy. [Kanski JJ and Bowling B. Clinical Ophthalmology: A Systematic Approach. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7, Lancet 2012;379:1728-38] Fundus autofluorescence imaging is another new non-invasive method now increasingly used clinically for characterization of geographic atrophy. [Kanski JJ and Bowling B. Clinical Ophthalmology: A Systematic Approach. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7, Exudative ARMD. Available at: emedicine.medscape.com/article/1226030 Accessed on 5 December]

**Management**


Monotherapy with an anti-vascular endothelial growth factor drug (injected into the vitreous) is the current standard of care for wet ARMD. Pegaptanib was the first anti-VEGF agent authorized for ocular treatment. However, ranibizumab and bevacizumab are currently used. Ablation of the area of neovascularization with thermal laser (laser photocoagulation) or induction of vascular thrombosis by photodynamic therapy PDT) with verteporfin, though less effective than anti-VEGF therapy, remain useful under certain clinical settings, particularly when anti-VEGF therapy is contraindicated or ineffective. [Kanski JJ and Bowling B. Clinical Ophthalmology: A Systematic Approach. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7, BMJ 2010; 340:c981] Combination therapy includes variations of anti-VEGF agents, PDT and steroids. [Kanski JJ and Bowling B. Clinical Ophthalmology: A Systematic Approach. 7th ed. UK: Elsevier Saunders; 2011:611-6, 620-7]

Visual impairment from AMD can lead to significant functional loss, reduced quality of life and depression. Early detection and prevention are critical. Any patients who present with blurring, distortion or loss of central vision should be promptly referred to an ophthalmologist.
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Location: Nice, France
Info: EAACI FAAM 2013 Secretariat
Tel: (33) 1 7039 3554
Fax: (33) 1 5385 8283
Email: infoFAAM2013@mci-group.com
Website: www.eaaci-faam.org/

International Meeting on Emerging Diseases and Surveillance (IMED 2013)
15/2/2013 to 18/2/2013
Location: Vienna, Austria
Info: International Society for Infectious Diseases
Tel: (617) 277 0551
Fax: (617) 278 9113
Email: info@isid.org
Website: www.isid.org/imed/Index.shtml

Asian Pacific Society of Cardiology 2013 Congress
21/2/2013 to 24/2/2013
Location: Pattaya, Thailand
Info: Kenes Asia (Thailand Office)
Tel: (66) 2 748-7881
Fax: (66) 2 748-7880
Email: apscoffice2013@apsc2013.org
Website: www2.kenes.com/apsc2013/pages/home.aspx

International Conference on Functional Biomedical Imaging
23/2/2013 to 24/2/2013
Location: Ho Chi Minh City, Vietnam
Info: SCIEI
Tel: (1) 6177166164
Email: icfbi@sciei.org
Website: www.icfbi.org

March

23rd Annual Meeting of the Society for Virology
Location: Kiel, Germany
Info: Conventus Congress Management & Marketing GmbH
Tel: (49) 3641 311 61 60
Fax: (49) 3641 311 62 43
Email: registrierung@conventus.de
Website: www.virology-meeting.de

3rd Emirates Hematology Conference
7/3/2013 to 9/3/2013
Location: Dubai, UAE
Info: Emirates Society of Haematology
Tel: (971) 4 4270492
Fax: (971) 4 4270493
Email: pco@ehc2013.com
Website: www.ehc2013.com

62nd American College of Cardiology (ACC) Annual Scientific Session
Location: San Francisco, California, US
Info: American College of Cardiology Foundation
Tel: (1) 415 800 699 5113
Email: accregistration@jspargo.com
Website: www.accscientificsession.org/Pages/home.aspx

28th Annual European Association of Urology Congress
15/3/2013 to 19/3/2013
Location: Milan, Italy
Info: European Association of Urology
Tel: (39) 2 4342 6275
Fax: (39) 2 4801 0270
Email: info@eaumilan2013.org
Website: www.eaumilan2013.org

65th American Academy of Neurology Annual Meeting
16/3/2013 to 23/3/2013
Location: San Diego, California, US
Info: American Academy of Neurology
Tel: (1) 612 928 6000
Fax: (1) 612 454 2746
Email: memberservices@aan.com
Website: www.aan.com

4th Biennial Congress of the Asian-Pacific Hepato-Pancreato-Biliary Association
27/3/2013 to 30/3/2013
Location: Shanghai, China
Info: Asian Pacific Hepato-Pancreato-Biliary Association
Tel: (86) 21 350 30066
Fax: (86) 21 655 62400
Email: secretariat@aphpba2013shanghai.org
Website: www.aphpba2013shanghai.org
UPCOMING

European Congress on Osteoporosis and Osteoarthritis
17/4/2013 to 20/4/2013
Location: Rome, Italy
Info: International Osteoporosis Foundation
Tel: (32) 4 254 1225
Email: info@iofbonehealth.org
Website: www.ecceo13-iof.org

48th European Association for the Study of the Liver
24/4/2013 to 28/4/2013
Location: Amsterdam, Netherlands
Info: European Association for the Study of the Liver
Tel: (31) 20 549 1212
Fax: (31) 20 646 4469
Email: devi.sonida-mey@easloffice.eu
Website: www.easl.eu/_the-International-liver-congress/general-information

5th Association of Southeast Asian Pain Societies Conference
28/4/2013 to 5/5/2013
Location: Singapore
Info: Pain Association of Singapore
Tel: (65) 6292 4710
Fax: (65) 6292 4721
Email: aseaps2013@kenes.com
Website: www.aseaps2013.org

American Urology Association (AUA) Annual Meeting
4/5/2013 to 8/5/2013
Location: San Diego, California, US
Info: AUA
Tel: (1) 410 689 3700
Fax: (1) 410 689 3800
Email: customerservice@AUAnet.org

World Congress of Nephrology
31/5/2013 to 4/6/2013
Location: Hong Kong
Info: ISN World Congress of Nephrology 2013
Tel: (852) 2559 9973
Fax: (852) 2547 9528
Email: registration@wcn2013.org
Website: www.wcn2013.org

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Are prestigious academic journals becoming less impactful?

New research shows an increasing disconnect between the number of times a scientific paper is cited and the impact factor (IF) of the journal in which it appears, pointing to a shift in how scientists consume and consider research. Radha Chitale reports.

Impact factor (IF) was conceived in the 1960s as a way to guide academic library purchases and evolved into an overall journal ranking system (zero is the lowest impact). A scientific journal’s IF is the average number of citations per published item in the 2 years preceding.

Historically, papers from journals with a high IF could be counted on to be cited more often than papers from journals with a low IF.

However, IF has become a controversial metric because determination criteria may not accurately reflect importance in the IF score. Greater free online access to individual papers is also subverting prestigious subscription-based journals’ corner on rigorous peer-reviewed literature.

“I think that there are plenty of ways to evaluate journals,” said lead researcher Dr. Vincent Lariviere of the University of Montreal’s School of Library and Information Sciences in Montreal, Quebec, Canada. “The IF is one of these – not the only one – [and] I think the digital era is breaking this.”

In an analysis of nearly 820 million citations and 30 million papers published between 1902 and 2009, Lariviere and colleagues found that “the relationship between the IF and citation rates has been weakening.” [J Am Soc Inf Sci 2012;63:2140-2145]

The researchers identified the break at about 1990, when they note that scientific information began to be disseminated electronically.

“In 1990, 45 percent of the top 5 percent most cited articles were published in the top 5 percent highest impact factor journals. In 2009, this rate was only 36 percent,” Lariviere said. “This means that the most cited articles are published less exclusively in high impact factor journals.”

The researchers said IF is imperfect for a number of reasons. Cited letters and commentaries count towards citations but not as “papers”, which can inflate the IF. Journal inclusion for scoring is at the discretion of a private data company. A niche journal or a new journal also has a lower chance of receiving a high IF, no matter the importance of the content.

“Even more troubling is the three-step approach of using the IF to infer journal quality, extend it to the papers therein, and then use it to evaluate researchers,” they said.

The IF was developed by an information scientist named Dr. Eugene Garfield for a citation index that was later acquired by what is now the media and financial data firm Thomson Reuters, the company that continues to curate the IF journal inclusion list.

On a few occasions, including a 2006 article in the Journal of the American Medical Association, Garfield allowed that the system is flawed.

“Impact Factor is not a perfect tool to measure the quality of articles but there is nothing better and it has the advantage of already being in existence and is, therefore, a good technique for scientific evaluation... Experience has shown that in each specialty the best
journals are those in which it is most difficult to have an article accepted, and these are the journals that have a high impact factor.” [JAMA 2006;295:90-93]

Some scientists echo the sentiment that a high IF journal is synonymous with a more rigorous standard of evaluation or the most important or cutting-edge research.

“I will automatically read and cite the journals with the highest IF and I submit to the highest IF journals,” said Assistant Professor Carolyn Lam of the National University Heart Centre, Singapore. “It is part prestige, and how we are graded as academics, but research is more likely to get cited if it is published in a high impact journal.”

Professor Teo Eng Kiong, editor-in-chief of the Singapore Medical Journal, said IF is important because “it serves as a composite measure of the relevance of the journal to the scientific committee.”

As a peer reviewer, Dr. Juliana Chan, a post-doctoral researcher at the Molecular Engineering Lab, Science and Engineering Institutes at Singapore’s Agency for Science Technology And Research (A*STAR), said that IF might help her predict what to expect from a piece of research.

“For example, if the IF of a journal is 1 versus 10, I would place equal scrutiny on the data but I would have a different set of expectations when giving my review.”

Chan said she does consider a journal’s IF when choosing what to read or where to publish, and skews towards high IF journals.

But scientists maintain the parallel view that open access research is just as important as publishing in high impact journals for getting cited, particularly in resource-poor countries.

As the Editor-In-Chief of the new ASEAN Heart Journal – which has no IF as yet – Lam noted the need for availability.

“Here you see me take a different stance. Our audiences are Southeast Asian nations who may not be subscribed to big publishing houses. We have to find a niche and have open access papers that are the best available online…. it impacts how often articles get cited, which in turn impacts the journal’s IF.”

Recognizing this, many big name journals and publishers have developed ways to free up content after a certain period of time.

Research supported by the US National Institutes of Health, for example, must be made free to the public within 12 months of publication, no matter where it appears.

“There used to be a strong difference between open and closed access, but not anymore.” Chan said. “Closed access is semi-open already.”

Prioritizing important subject matter may also be a more beneficial model for readers who find material outside of large journals.

“Going forward, it may be the publishing pattern of authors to decrease the emphasis mainly on IF rather than the relevance of the journal to their article,” Teo said. “Eg, choosing to publish in the Journal of Gastroenterology and Hepatology rather than Gastroenterology for Asian patients – lower impact, but more geographical relevance.”

Although scientists acknowledge that IF is not perfect, they maintain that it will likely persist as there will always be a place for a ranking system in academic publishing. The results from Lariviere and colleagues may show that the correlation between citations and high IF is weakening but the historical assumption that research from a high IF journal is of a certain standard remains.

“It’s possible to read extremely good research in low impact journals and to read bad research in high impact journals,” Chan said. “But it’s a trend that a high impact journal will lead to a better paper.”
“My husband is not feeling well. He complains about his knees, his back, just about everything. Where do you think I can find a pair of earplugs?”

“Wait a minute! Did you by any chance touch those little things on my desk that look like candy?”

“Allow me to introduce myselfs!”

“It’s your dentist Larry. He’s here to remind you that it’s been 6 years!”

“A date with Pamela Anderson? By all means, go for it!”

“If you are afraid of catching the flu, perhaps you should stay home!”

“That anger management group you recommended ... Well, I was there and it made me very angry!”

“If you are afraid of catching the flu, perhaps you should stay home!”

“It’s your dentist Larry. He’s here to remind you that it’s been 6 years!”

“A date with Pamela Anderson? By all means, go for it!”

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