INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

March 2019

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NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2019

Clinical Research Protocol Writing Workshop

(CRIPIK 2019) @ Holiday Inn Hotel, Kemayoran

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INA-RESPOND Secretariat

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INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: ANANDIKA PAWITRI, EKA WINDARI R., LOIS E. BANG, MARIA INTAN JOSI, M. IKHSAN JUFRI, VENTY MULIANA SARI

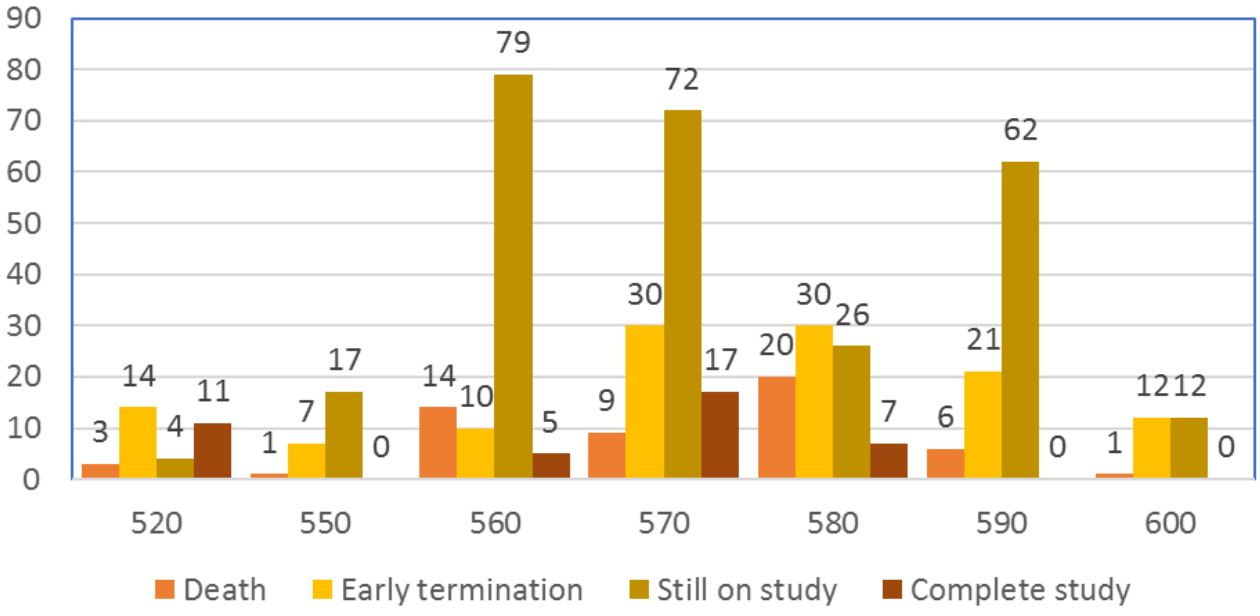

Figure 1. Participants Status Per Site Based On Uploaded CRF per 8 March 2019

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PARTICIPANT STATUS

Per 8 March 2019, the total number of ongoing participants in TRIPOD study is 272 out of 490 enrolled participants. 40 participants have completed the study and 178 participants are early-terminated (including death). Therefore, there are still 55.5 % participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are 4 participants from site 520 (RS Sanglah Denpasar) who still need to be followed up, 17 participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 79 participants from site 560 (RSUP dr. Kariadi Semarang), 72 participants from site 570 (RSUD dr. Soetomo Surabaya), 26 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 62 participants from site 590 (RSUP Persahabatan Jakarta), and 12 participants from site 600 (RSUP dr. Adam Malik Medan).

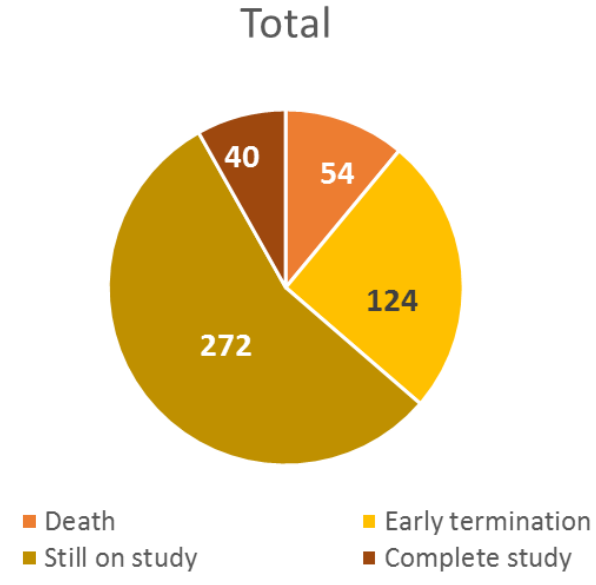

Figure 2. Total Participants Status based on uploaded CRF per 8 March 2019

Site	Waiting for Baseline Culture Result	Waiting for Baseline DST Result
520 (n=32)	Complete	Complete
550 (n=25)	Complete	Complete
560 (n=108)	4 (estimation: Feb 2019)	40 (estimation: Feb 2019)
570 (n=128)	14 (estimation: Feb 2019)	25 (estimation: Feb 2019)
580 (n=83)	5 (estimation: Feb 2019)	6 (estimation: Feb 2019)
590 (n=89)	24 (estimation: Feb 2019)	24 (estimation: Feb 2019)
600 (n=25)	1 (estimation: Feb 2019)	1 (estimation: Feb 2019)

Figure 3. Culture and DST result up to 8 March 2019.

AWAITING CULTURE AND DST RESULT

Not all sites have all the baseline culture and drug susceptibility testing (DST) results. As we can see from the table, site 520 (RS Sanglah Denpasar) and site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) have all test results.

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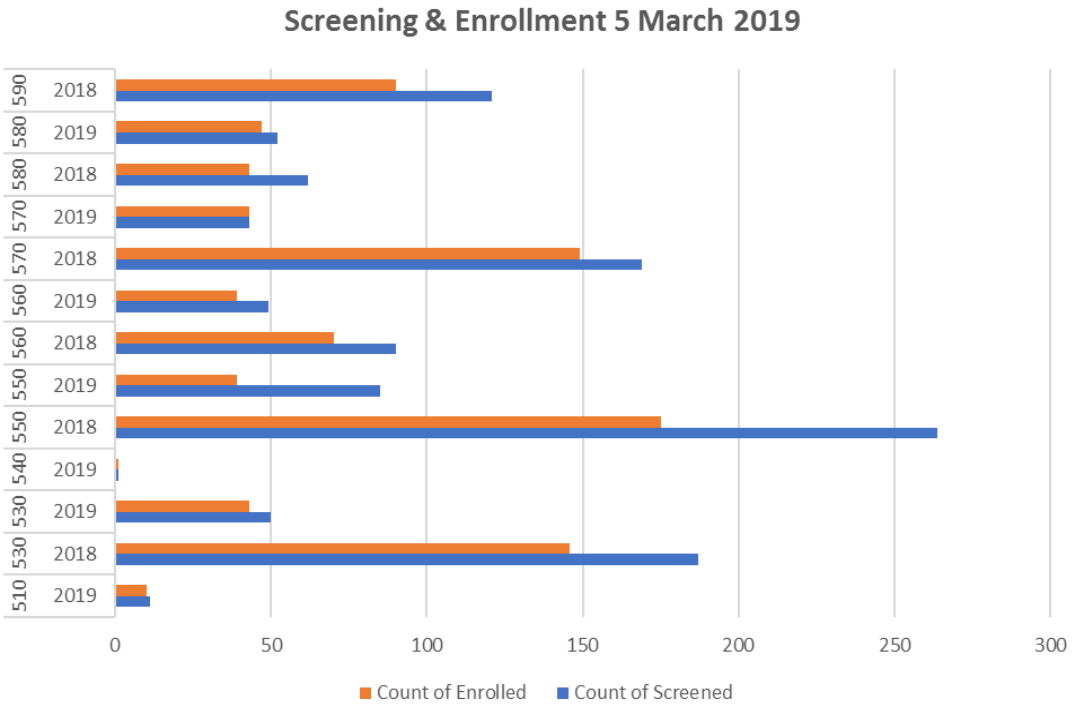

One new site (site 540 – RSPI Sulianti Saroso, Jakarta) was activated on 18 February 2019. This site enrolled its first subject on 25 February 2019. Also, Site 510 (RSUP dr Hasan Sadikin, Bandung) enrolled its first subject on 7 February 2019. Therefore, up to now 14 sites actively enrolled subject for this study.

By 5 March 2019, the total number of enrolled subjects from all sites is 1,781, consisting of 83 paediatrics and 1,697 adults. Sites enrolled 63.15% of screened patients (2,820 screened patients). The enrollment failure rate was 36.84% from total screening.

A team from INA-RESPOND Secretariat, Jakarta visited site 670 (RSUD dr Zainoel Abidin, Banda Aceh) for Site Preparation Visit (SPV) on 19-21 Feb 2019 and Site Initiation Visit (SIV) on 5-6 Mar 2019. This site is planned to be activated by April 2019. CRA is also coordinating with site 680 (RSUD dr. Soedarso, Pontianak) for its SIV. In addition, site assessment visit was conducted at TC Hillers Hospital, East Nusa Tenggara on 1 Mar 2019.

A site monitoring visit (SMV) will be conducted at site 510 (RSUP dr Hasan Sadikin, Bandung) on 11-12 Mar 2019, at site 560 (RSUP dr Kariadi, Semarang) on 12-14 Mar 2019, and at site 550 (RSUP dr Wahidin Sudirohusodo, Makassar) on 18-20 Mar 2019.

INA-RESPOND Newsletter

TECHNICAL SURVEILLANCE MEETING ON HANTAVIRUS

By: M. HELMI AZIZ & NURHAYATI

REPORTS

On 11 March 2019, INA-RESPOND was invited by *Direktorat Jenderal Pencegahan dan Pengendalian Penyakit (Ditjen P2P)* to share information on Hantavirus finding in the AFIRE study. The meeting aims to help the government to develop a guidance for technical surveillance on Hantaviruses in Indonesia. So, why are Hantaviruses important to discuss? This report will share the findings related to Hantaviruses in human and rodent across Indonesia.

The first human cases of Hantaviruses were reported in port town, Maumere in 1991. Five years later, in 1996, other cases of Hantaviruses were also reported in the port area in Tanjung Priuk and Sunda Kelapa. The surveillance of Hantaviruses along with other rodent-borne viruses, Leptospira, was conducted in sentinel areas throughout Indonesia to follow up on the reports,. The results of the surveillance in 2017 showed that the total prevalence of Hantaviruses in rodent in Indonesia was 6.08% with DKI Jakarta as the most prevalent area (23.81% for Hantaviruses and 33% for Leptospira spp.). Also, another study conducted in Maumere in 2014 showed that the prevalence of *Leptospira spp.* in *Rattus norvegicus* was 4.3%, Hantaviruses was 22.8%, and dual infection of both was 1.8%.

The rodent surveillance also showed that 15 murine that live in 26 provinces in Indonesia have been proven to carry several Hantaviruses such as Seoul virus, Thottapalaya virus, Serang virus, and Thailand Hantavirus. Another interesting finding is that rodents consumed as food in North Sulawesi have been found to carry Hantaviruses. However, researchers must dig deeper to conclude whether food transmission is responsible for Hantaviruses transmission.

So, why is it that despite the high prevalence and evidence of Hantaviruses in rodents, we rarely find human cases of Hantaviruses in Indonesia?

The first possible answer is because Hantaviruses infection in Indonesia is considered to have mild symptoms unlike the Hantaviruses infection that occurs in North America. The second probable answer is because our hospital or primary health centre do not have the capacity to diagnose Hantaviruses infection in patients. Also, Hantaviruses infection does not have

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INA-RESPOND Newsletter

FINDING FUNDING FOR YOUR RESEARCH

By: AARON NEAL, DPhil

Conducting clinical and biomedical research is challenging for many reasons: complex scientific questions, extensive study logistics, and complicated diagnostic tests and lab assays, just to name a few. Unfortunately, one of the biggest challenges for any investigator is the high cost of research and the need to acquire independent funding. Financial support for research can come in many forms, but investigator-initiated studies are most commonly funded through grants. Groups like the US NIH, US NSF, USAID, Wellcome Trust, and Bill & Melinda Gates Foundation routinely solicit and review study proposals, selecting only a small percentage to ultimately fund. While there are many factors that shape a highly-competitive, fundable research proposal, a critical step in the preparation process is identifying an appropriate funding opportunity.

Before beginning a search for funding, investigators should identify the following key features of the planned study and use them to optimize the search process: study topic/size/duration/location/start, estimated budget, investigator experience, and clinical trial or not. Additionally, investigators should consider whether they are eligible for special categories of grants, such as new investigator awards, low/low-middle income country (LMIC) awards, and region-specific awards. While these special category grants are often smaller in size and duration, they are generally less competitive and have simpler applications.

Grant opportunities typically fall into the categories of investigator-initiated, where a specific research topic and/or approach is not required by the funder, and solicited, where a research topic and/or approach is required and specified by the funder. Investigator-initiated awards are typically funded by government agencies, such as the US NIH, and are often very competitive since there are fewer restrictions on who can apply. Solicited awards are funded by both

governments and private organizations, such as the Bill & Melinda Gates Foundation, and can be less competitive since applications are restricted to certain topics and/or study types. Starting a funding search with a research topic in mind optimizes an investigator's chance of finding the grant opportunity with the highest chance of success.

Once a category of grant has been identified, it becomes important to consider the size and duration of the award and how they align with the proposed study. NIAID general research awards, or R awards, have various requirements and come in different sizes/durations, so an investigator may choose to apply for an R01 instead of an R03 if the proposed study is planned for 3 years. The sizes and durations of solicited

awards vary from opportunity to opportunity, but investigators should remain flexible and consider adapting their study to fit an ideal funding opportunity if it means the study will be funded.

Of particular interest to Indonesian investigators should be region-specific and LMIC grants. These types of awards are generally less competitive, and the infectious disease research interests of INA-RESPOND investigators often fit perfectly within the scope of the opportunities. Region-specific awards include the U.S.-Japan Cooperative Medical Science Program, which funds collaborative research between Indonesian and U.S. investigators, the e-ASIA Joint Research Program, which funds collaborative research in the Southeast Asia and Asia-Pacific regions, and the USAID PEER Program, which funds independent research that falls within USAID country priorities. LMIC awards, which Indonesian investigators are eligible for given Indonesia's classification by the World Bank, include many opportunities from the NIH Fogarty International Center, the Wellcome Trust, and ASTMH. Unlike general research grants, many LMIC awards also include special provisions for local capacity building, either through specific financial support, scientific mentorship, or training/travel opportunities.

Though the research funding process can seem overwhelming at times, it is important to remember that funding organizations truly want investigators to succeed. To help applicants navigate the complexities of the NIH grant system, NIAID provides comprehensive guides and examples on their website (links below). Additionally, NIAID research program staff, all of whom are scientists and clinicians themselves, are often available for consultations on the grant application process and the scientific priorities of NIAID. A great scientific idea that never leaves the computer does not benefit anyone, so I hope you use this short overview, the links below, and your Indonesian and American colleagues to begin finding the perfect grant and turning your idea into reality.

USAID PEER: http://sites.nationalacademies.org/pga/peer/index.htm

e-ASIA JRP: https://www.crdfglobal.org/funding-opportunities/e-ASIA

US-Japan: https://www.crdfglobal.org/funding-opportunities/2019-USJCMSP

NIH Fogarty: https://www.fic.nih.gov/Funding/Pages/default.aspx

Wellcome Trust: https://wellcome.ac.uk/funding

ASTMH: https://www.astmh.org/awards-fellowships-medals/astmh-sponsored-fellowships

Gates Grand Challenges: https://grandchallenges.org/grant-opportunities

All US Grants: https://www.grants.gov/web/grants/search-grants.html

NIAID: https://www.niaid.nih.gov/grants-contracts/find-funding-opportunity

Apply for an NIAID grant: https://www.niaid.nih.gov/grants-contracts/apply-grant

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any specific signs and symptoms. Therefore, it is hard to make Hantaviruses as differential diagnosis in patient care related settings. In our AFIRE studies, we found that 37 from 332 (11.1%) participants carried Hantaviruses IgG antibodies, which suggested that there had been an exposure to Hantaviruses in the past (unpublished data). The data that was displayed in the meeting will be used to develop technical guidance for Hantaviruses surveillance in Indonesia. The Hantaviruses surveillance will be integrated to *Leptospira spp.* sentinel surveillance that is currently running in Indonesia. The surveillance also aimed to improve the diagnostic capacity of Hantaviruses in several areas in Indonesia.

We hope that the Hantaviruses surveillance will be conducted soon and generate results that are useful to combat Hantaviruses in Indonesia. However, we need to consider that other rodent borne viruses such as Rickettsiosis and other Helminths infection also present and pose a threat to public health in Indonesia. An integrated all-rodent-borne disease surveillance (not only two diseases) will be beneficial for Indonesia to overcome public health problem related to rodents.

Relevant, novel, and feasible research study idea
General Grants (Investigator-Initiated) (Highly Competitive)
Topic-Specific Grants (Solicited) (Varying Competition)
LMIC-Specific Region-Specific (Investigator-Initiated or Solicited) (Less Competitive)
NIAID Independent Research Award
Government NIH/NIAID NSF USAID
Organizations Wellcome Trust Bill & Melinda Gates Foundation
Organizations ASTMH: LMIC Awards Wellcome Trust: LMIC Awards
Government NIAID: U.S.-Japan CMSP NIAID: e-ASIA JRP Fogarty: LMIC Awards USAID: PEER
R01 ≈$500,000 USD 4-5 years 22.1% Success Rate 2018
R03 <$100,000 USD 2 years 26.5% Success Rate 2018
R21 <$275,000 USD 2 years 21.5% Success Rate 2018

INA-RESPOND Newsletter

FROM OUR LABORATORY

VITAMIN D: THE MISSING VITAMIN IN OUR BODY

By: UMI S. INTANSARI

Vitamin D is a fat-soluble molecule which is largely produced in the skin with the help of sunlight. Vitamin D is obtained naturally through exposure of the skin to UVB rays, which will convert 7-dehydrocholesterol (pro-vitamin D3) to cholecalciferol (vitamin D3). The second source of vitamin D is from food intakes, namely by changing ergosterol (vitamin D2) in plants [1]. Cholecalciferol in the body is inactive and will immediately bind to vitamin D-binding proteins (VDBP) or albumin. It will then be converted to the active form in the circulation, namely calcitriol (1.25 dihydroxy vitamin D [1.25(OH)2D]) by enzymes 1-α-hydroxylase (CYP27B1) (Figure 1). Serum 25(OH)D level is considered to be the most accurate marker for determining vitamin D status [2–5]. The Endocrine Society agrees that levels below 20ng/mL (50 nmol/L) are considered deficient, levels of 20-29.9 ng/mL (52-72 nmol/L) is deemed insufficient, and levels above 30 ng/mL (75 nmol/L) are considered sufficient. Institute of Medicine (IOM) states that the levels >20 ng/mL are deemed to be enough in the general population [6].

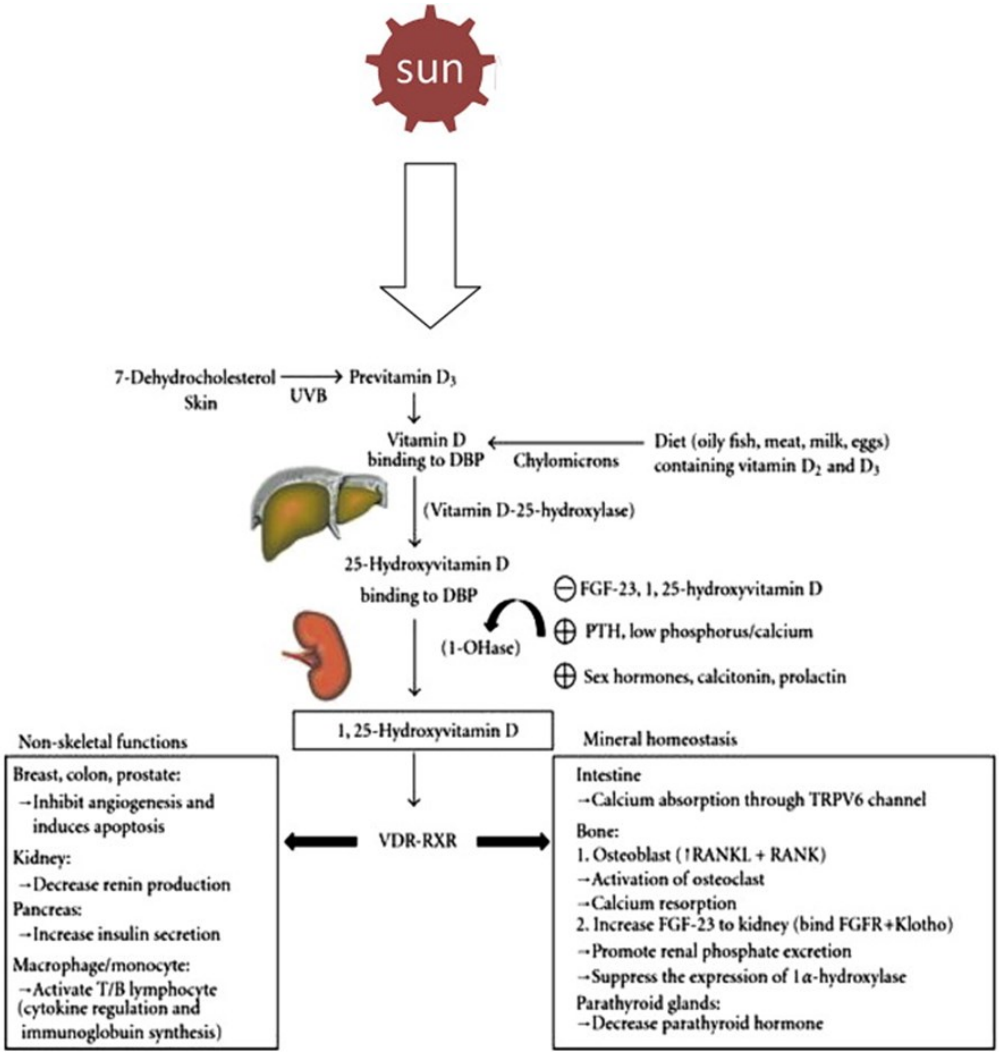
Only a few foods contain vitamin D. Cod oil is a good source of vitamin D, but consumption in large quantities can lead to vitamin A toxicity. The best way to get vitamin D is by supplementation. Lots of multivitamins circulating contains 800-1000 IU of vitamin D. Guide from the Endocrine Society of Clinical Practice stated that the maximum vitamin D intake in adults is 1500 IU per day [7.8].

Vitamin D is mainly involved in calcium metabolism which is vital in maintaining bone structure. In the immune system, vitamin D regulates the inflammatory response. Vitamin D deficiency occurs in nearly 50% of the population in the world. Vitamin D deficiency pandemic can occur due to lifestyle (such as rarely doing outdoor activities) and the environment (such as air pollution). These causes result in reduced sunlight containing ultraviolet B, which decreases the production of vitamin D in the skin. Vitamin D deficiency occurs in cancer, bone disorders, metabolic disorders, and autoimmune diseases [4,7].

In recent years more and more studies have tried to examine the role of vitamin D in the immune system. Until 1980, the function of vitamin D had been widely known to play a role in calcium, phosphate, and bone mineral metabolism [9]. Vitamin D affects immune modulation and is involved in the proliferation and differentiation of natural and adaptive immune cells. Vitamin D deficiency is associated with susceptibility to infection, for example, upper respiratory tract infections, influenza, bacterial vaginosis and HIV [10–12].

Vitamin D inhibits proliferation, B cell differentiation, and immunoglobulin secretion [13,14]. Against T cells, vitamin D suppresses proliferation and causes a phenotypic shift from T-helper 1 (Th1) to T-helper 2 (Th2) [3,15] and affects T cell maturation by changing the Th17 phenotype [16]. Vitamin D is also known to inhibit T cell cytokines such as IL-2 and IL-17 and increase the production of anti-inflammatory cytokines, such as IL-10 [5]. Supplementation with high doses of vitamin D in healthy humans (1ug twice daily for seven days) decreases proinflammatory cytokines IL-6 produced by peripheral mononuclear cells so that it has a positive effect on the body. Vitamin D also affects monocytes and dendritic cells, by inhibiting production of inflammatory cytokines by monocytes such as IL-1, IL- 6, IL-8, IL-12, and TNF-α [9,16]. Thus, vitamin D plays a role in maintaining self-tolerance to prevent the occurrence of autoimmunity.

Some chronic diseases are believed to be related to the role of vitamin D. Patients with cardiovascular disorders such as heart failure and hypertension have low levels of vitamin D in the blood. Vitamin D is considered to play a role in the balance of hormones that play a role in the cardiovascular function and have a protective effect on the heart and blood vessels. Patients with vitamin D supplementation also have lower sugar levels. Vitamin D prevents abnormal cell growth, which can reduce cancer risk [7,17].



7-Dehydrocholesterol with the help of sunlight is converted into pre-vitamin D3, which will then be turned in the liver and spleen to become an active metabolite form (1.25-Hydroxyvitamin D)

UVB = Ultraviolet B ray, DBP = VD Binding Protein, FGF = Fibroblast Growth Factor,

PTH = Parathormone, VDR = VD Receptor, RANK = receptor activation of NF-kB [(1)]

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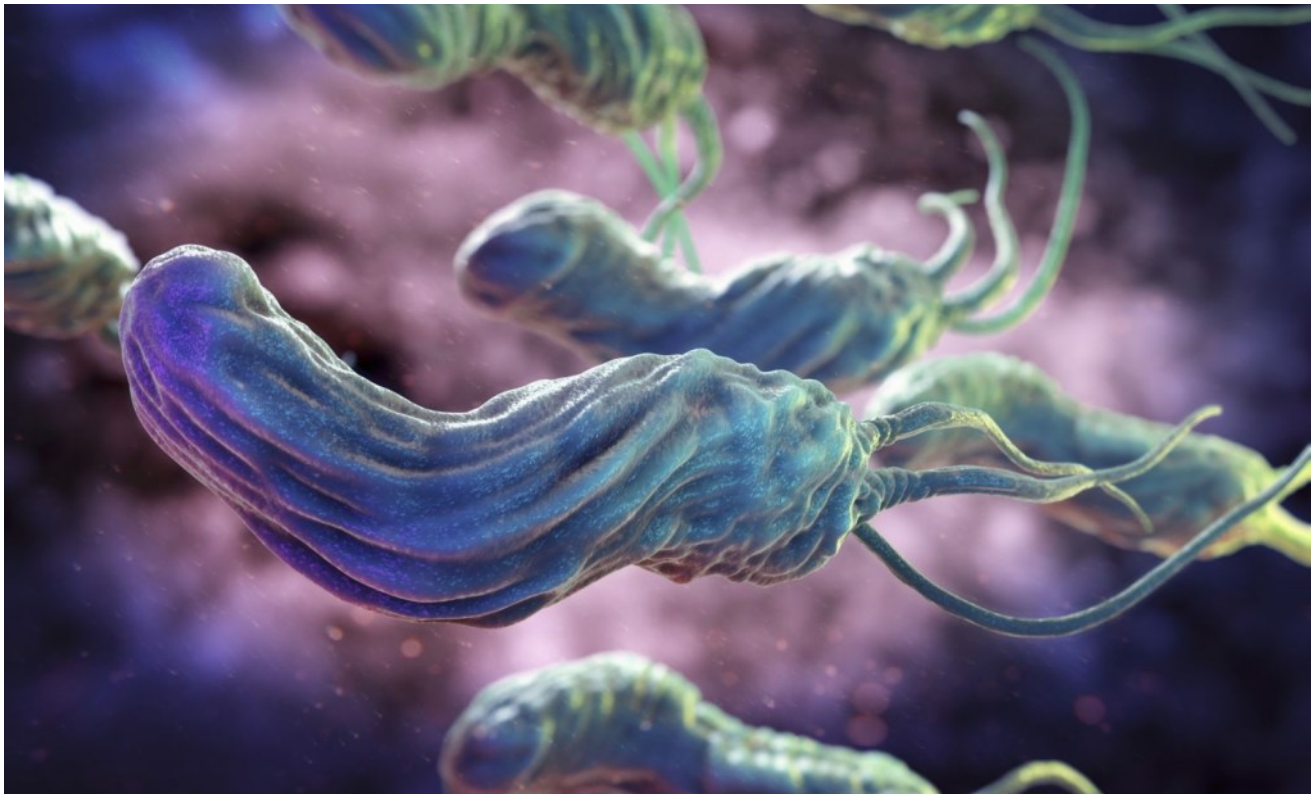
INA-RESPOND Newsletter

Helicobacter Pylori and Type II Diabetes

By: M. HELMI AZIZ



SCIENCE & HEALTH

A non-communicable disease, such as type 2 diabetes mellitus (T2DM) is a major and growing problem worldwide. It is estimated that the number of people with diabetes will rise from 415 million in 2015 to 642 million in 2040 [1]. The pathogenesis of T2DM is complex but mostly focused on insulin resistance and impaired pancreatic β-cell function. Insulin resistance is affected by many factors, some of them are inherited, and others are modifiable. The modifiable factors include physiological conditions and environmental factors, including obesity, sedentary lifestyle, chronic inflammation, and infections. The two latter factors have been linked to infection of the gram-negative, spiral-shaped pathogenic bacterium, called Helicobacter pylori (H. pylori) [1, 2]. However, how do the bacteria that colonize the gastric epithelium contribute to the development of T2DM? This month's article will review the pathogenesis of T2DM contributed by H. pylori infection.

The relationship between H. pylori infection and diabetes remains controversial. Some studies indicate a higher prevalence of H. pylori infection in diabetic patients, while others do not. In 1989, Simon showed that the prevalence of H. pylori infection in patients with diabetes was higher than asymptomatic controls (62% and 21% respectively) [2]. However, the study was considered controversial since only one rapid urease test was used to detect the presence of H. pylori. Although there is no solid evidence of H. pylori role in diabetes mellitus, there are several pathogenic mechanisms of the bacteria that promote the development of T2DM.

H. pylori Promote Insulin Resistance and Decrease Insulin Secretion

Insulin resistance is defined as a state where insulin can no longer effectively induce glucose disposal in skeletal muscle or suppress endogenous glucose production in the liver. The first evidence of the association between H. pylori and insulin resistance was shown by higher homeostatic model assessment-estimated insulin resistance (HOMA-IR) scores in H. pylori-positive individuals [(2)]. However, some studies showed that there was no consistent association between H. pylori infection and insulin resistance variables, even after H. pylori eradication [(2)]. Decreased insulin secretion is one of the major pathophysiologies in T2DM due to the defects in β-cell function. A study conducted in Chinese men showed that H. pylori titer could independently predict abnormal pancreatic β-cell functions. Also, another study supports that H. pylori infection has a positive association with impaired insulin secretion. The insulin resistance and decrease insulin secretion in H. pylori infection were thought due to the result of inflammation and oxidative stress. However, all of the studies aforementioned only showed epidemiological proof. The exact mechanism of insulin resistance and decreased insulin secretion in H. pylori infection need further investigation.

H. pylori and Inflammation

It is believed that chronic inflammation that is induced by H. pylori infection is strongly correlated to the pathogenesis of T2DM. Activation of the innate immune system and chronic-low-grade inflammation mediated by cytokine are the major explanation of T2DM occurrence [(2)]. The inflammation of the adipose tissue is the key to the T2DM pathogenesis of insulin resistance and β-cell autoinflammation that is mediated by interleukin-1β (IL-1β) [(2)]. The inflammation is characterized by macrophage infiltration and increased expression of chemokines and cytokines (Human CRP, IL-6, and Tumor Necrosis Factor (TNF)). These substances along with macrophage-secreted factors secrete paracrine effects that result in the activation of serine kinases and the inhibitor of nuclear factor kappa B kinase β, which phosphorylates insulin receptor substrate proteins and creates a state of insulin resistance in adipose tissue [(2)]. Also, the proinflammatory cytokines have direct inhibitory effects on glucose transporter protein GLUT4, insulin receptor substrates, and glucose-stimulated insulin release by pancreatic β-cells [(2)].

Moreover, the colonization of H. pylori in gastric epithelium induce chronic inflammation that attracts neutrophils and monocytes to infiltrate gastric submucosal, which later alter the gut microbiota composition. The change in the composition leads to the increased production of lipopolysaccharide [(2)]. Lipopolysaccharide is well known to promote activation of the innate inflammatory response. The concentration of circulating lipopolysaccharide is higher in obese patients with T2Dm than in non-diabetic-lean individuals and associated with the insulin resistance [(2)].

H. pylori and Hormones Regulation

Gastric-related hormones such as leptin, ghrelin, gastrin, and somatostatin are affected by the presence of H. pylori [(2)]. Gastrin increases food-related and glucose-stimulated insulin release. Meanwhile, somatostatin regulates pancreatic insulin secretion and inhibits insulin release [(2)]. During H. pylori infection, the basal and stimulated concentration of gastrin increases and the concentration of somatostatin decreases [(2)]. Leptin and ghrelin are two hormones produced in the stomach and involved in energy homeostasis [(2)]. Ghrelin functions are to decrease energy expenditure and promote weight gain. Meanwhile, leptin reduces food intake and increases energy expenditure [(2)]. H. pylori can impair ghrelin production and enhance leptin production. The imbalance of ghrelin and leptin levels leads to obesity and insulin resistance thus promotes the development of diabetes [(2)].

Now that we know there is a connection between H. pylori and the development of T2DM, how does H. pylori treatment affect T2DM patients? Studies showed that H. pylori treatment could decrease the HbA1C levels, fasting insulin levels, HOMA-IR levels, and the metabolic abnormalities in patients with T2DM. However, conflicting results were also shown by other studies related to H. pylori treatment in T2DM patients. In conclusion, although much research seems to point out the relationship between H. pylori and T2DM, further studies are needed to strengthen the association and to obtain the causative link between both.

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INA-RESPOND Newsletter

Exercise During Pregnancy: Baby, Let's Move!

By: MONICA SURJANTO

dr. Monica Surjanto
Sports Medicine Resident
at *Universitas Indonesia*

Many pregnant women are reluctant to do physical activities or work out because they are worried that the activities/ exercise may harm the pregnancy. This thinking can make pregnant women sedentary, which eventually raise adverse health issues, such as gestational diabetes, hypertension, and mental stress. Contrary to what most women think, exercising during pregnancy is safe and healthy for the mother and the baby if the types of activity are right, and we know the precautions and contraindications for doing the exercise. The American College of Obstetrics and Gynecology (ACOG) recommends that in the absence of obstetric or medical contraindications, pregnant women should be encouraged to engage in regular, moderate-intensity physical activities during pregnancy. Many common complaints of pregnancy, including fatigue, varicosities, and swelling of the extremities, are reduced in women who exercise.[1]

Benefits of exercise during pregnancy

Physical activity and exercise during pregnancy provide various health benefits. Pelvic floor muscle training (Kegel exercise) results in improved muscular control and flexibility. This exercise also prevents urinary incontinence during pregnancy and after childbirth. A cohort study of pregnant women in Norway showed that physical activity during pregnancy, such as walking, commuting to work by bike, and sports/exercise between the pregnancy had a clinically significant reduction in pelvic girdle pain, low back pain, and depression. Another study by Silveira & Segre showed that women who regularly did the stretching and strengthening exercises had a higher rate of vaginal deliveries or a lower rate of caesarean sections and had more aerobic fitness, muscular strength, reduced time for the birth, and reduced risk of childbirth complications. Moreover, trained women recovered faster postpartum and had a better profile of pregnancy-related medical conditions such as high blood pressure and blood sugar than the women who did not train.[2]

Excessive weight gain in pregnancy is associated with gestational diabetes, preeclampsia, and postpartum weight retention. In 2013, ACOG endorsed the Institute of Medicine's weight gain goals during pregnancy based on a woman's body mass index (BMI) at her first prenatal visit. According to these recommendations, women with a normal BMI (18.5-24.9 kg/m^2) should gain 11 to 16 kilograms whereas overweight (BMI 25-29.9 kg/m^2) and obese (BMI >30 kg/m^2) women should aim to gain 7 to 11 kilograms and 5 to 9 kilograms, respectively. Exercise can help manage weight gain during pregnancy.[3]

Prescription of pregnancy exercise

During pregnancy, the center of gravity moves forward, and this can cause poor postural control, which can affect physical performance. Activities that include rhythmic and dynamic movement of major muscle groups such as brisk walks, swimming, water gymnastics, climbing stairs/step-ups, aerobic dance, and cycling are recommended. Tai chi and some forms of yoga are other good options when they facilitate relaxation and increase body awareness.[2]

The best time to progress is during the second trimester since risks and discomforts of pregnancy are the lowest at that time. Aerobic exercise should be increased gradually from a minimum of 15 minutes per session, three times per week to a maximum of approximately 30 minutes per session, four times per week.[4]

Check the accuracy of the heart rate target zone by comparing it to the RPE scale on the right. A range of about 12 -14 (somewhat hard) is appropriate for most pregnant women.

For pregnant women aged 18-45 years, 8-10 muscle strengthening exercises can be performed over one to two sessions per week (non-consecutive days). Heavyweights may overload joints already loosened by increased levels of the hormone during pregnancy. It would be wise to use lighter weights and do more repetitions instead. One should be careful with free weights as free weights may involve the risk of hitting the abdomen. As an alternative, pregnant women can use resistance bands which offer different amount of resistance and more varied ways to do weight training. The use of these bands should pose minimal risk to the stomach.[5]

Contraindication and safety considerations for exercise during pregnancy

There are some medical conditions where exercise should be avoided. Absolute contraindications, such as ruptured membranes in premature labor, placenta previa, pre-eclampsia, incompetent cervix, evidence of intrauterine growth restriction, high-order pregnancy (e.g., triplets), uncontrolled type-1 diabetes, hypertension or thyroid disease, other severe cardiovascular, and respiratory or systemic disorder. For the relative contraindications, such as anemia, malnutrition, twin pregnancy after the 28th week, history of spontaneous abortion/premature labor in previous pregnancies, women should consult with their doctor first before doing any exercise.[4]

Safety considerations for exercise during pregnancy

Avoid doing exercise in warm/humid environments, especially during the 1st trimester.

Avoid isometric exercise or straining while holding your breath.

Maintain adequate nutrition and hydration. It is recommended to drink six to eight glasses of fluid, including water each day and limit caffeine intake (coffee, tea).

Avoid exercise while lying on your back past the 4th month of pregnancy. Lying on your back may cause the uterus to compress a major vein, the inferior vena cava which blood from the pregnant uterus flows.

Know the reasons to stop exercise (excessive shortness of breath, chest pain, painful uterine contractions more than six to eight times per hour, vaginal bleeding, any "gush" of fluid from vagina, dizziness or faintness), and immediately consult with a qualified health care provider if they occur.

During pregnancy, the need for calories is higher (about 300 kcal more per day) than before pregnancy. Choose healthy food from the following groups: whole grain or enriched bread or cereal, fruits, vegetables, milk, milk products, meat, fish, and poultry. Remember that it is normal to gain weight during pregnancy, so dieting to lose weight is not recommended.

Conclusion

Exercise during pregnancy should be encouraged for all women who do not have contraindications. Known benefits of exercise apply during pregnancy, and there are few absolute and relative contraindications. Regular obstetric visits should be used to monitor progress, avoiding dehydration and overexertion while watching thermoregulation and caloric intake, and adapting exercise regimens based on changes during pregnancy is needed. Enjoy your pregnancy as a unique and meaningful experience.

F **FREQUENCY**
Begin at 3 times per week and progress to four times per week

I **INTENSITY**
Exercise within an appropriate RPE range and/or target heart rate zone

T **TIME**
Attempt 15 minutes, even if it means reducing the intensity. Rest intervals may be helpful

T **TYPE**
Non weight-bearing or low-impact endurance exercise using large muscle groups (e.g., walking, stationary cycling, swimming, aquatic exercises, low impact aerobics)

HEART RATE RANGES FOR PREGNANT WOMEN

MATERNAL AGE	FITNESS LEVEL OR BMI	HEART RATE RANGE (beats/minute)
Less than 20	–	140-155
20-29	Low	129-144
	Active	135-150
	Fit	145-160
	BMI > 25kg m^{-2}	102-124
30-39	Low	128-144
	Active	130-145
	Fit	140-156
	BMI > 25kg m^{-2}	101-120

Target HR ranges were derived from peak exercise tests in medically prescreened low-risk women who were pregnant. (Mottola et al., 2006; Davenport et al., 2008).

RATING OF PERCEIVED EXERTION (EPE)

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INA-RESPOND Newsletter

Enriching Our Vocabulary Through Collocations

By: DEDY HIDAYAT

As a non-native English user, we sometimes have difficulties understanding or using words in English the right way. These difficulties often lead to weird-sounding kind of errors in our speeches or sentences like "I will do a healthy lifestyle," "I was late because there was hard traffic on my way to the office," "The deep article discusses the issue in great details," or "I've made a large mistake." Even though most people will be able to understand what we mean when we say or write these sentences, native English users do not generally make these mistakes.

So, why do the sentences in the paragraph above sound weird? Well, the answer to that is because native English users do not say "do a lifestyle," "hard traffic," or "a large mistake." They normally say, "have a (healthy) lifestyle," "heavy traffic," "in-depth article," and "big mistake." Just like in the Indonesian language, English has words that fit together, and others that do not. We call this, collocations. Collocation is "the habitual juxtaposition of a particular word with another word or words with a frequency greater than chance"; or in other words, a pair or group of words that are usually put together.

Collocation Patterns

Forming collocations can be tricky because there may be other possible combinations. Look at the example of "have a (healthy) lifestyle." With the word lifestyle, we can also say lead a healthy lifestyle or enjoy a comforta-

ble lifestyle. Also we can use the word in a phrase and say "a change in lifestyle." The combinations do not have any logic to them, and this makes collocation rather hard. If you do not know that have a lifestyle is the right collocation, it is hard to guess.

Don't be discouraged, though. You may have known lots of collocation already. Look at the collocation patterns below and see if you have recognized most of the given examples, then think of a word related to your work or life and form collocations using the patterns.

- **Adjective** + **Noun**: detailed/in-depth/extensive/further/ground-breaking/pioneering/collaborative/empirical/academic/clinical/medical/scientific/social research
- **Noun** + **Noun**: research degree/effort/programme/project/methods/findings/results/purposes/centre/institute/laboratory/group/team/grant
- **Noun** + **Verb**: research demonstrate/indicate/prove/reveal/suggest/produce (something)
- **Verb** + **Noun**: carry out/conduct/do/undertake/is based on research
- **Verb** + **Expression with Preposition**: research for/into; look at/towards/like/to/into
- **Verb** + **Adverb**: has been poorly/meticulously/properly/thoroughly researched
- **Adverb** + **Adjective**: completely/extremely/far from/not entirely satisfied

Collocation VS Phrasal Verb

As part of collocations, phrasal verbs can be an effective means for building our vocabulary. Interestingly, people often confuse collocations with phrasal verbs. This is quite normal as we have learned that collocations have many possible combinations. So, what is a phrasal verb and how is it different from a collocation?

In general, collocations include many different types of word combination, for example, noun-noun combinations, verb-noun combinations, etc. However, phrasal verbs have a very specific definition: they are made of a verb plus an adverb or a preposition, and the whole phrasal verb has a meaning which is not necessarily connected to either part. For example, the meaning of 'turn up' has no literal connection to the meanings of 'turn' and 'up'. This fact makes learning phrasal verbs beneficial to expanding our vocabulary.

The following are some examples of phrasal verbs.

- I *broke out* in a rash after eating some strawberries.
- She can't *put off* going to the doctor any longer.
- The monitor *sees to* it that the study goes according to the protocol and ICH-GCP.
- The study team is trying to *figure out* how to increase the participant enrolment number.

Did you notice how the meaning of the individual word differs from the meaning of the combined words (phrasal verb)*? Now, imagine how much our writing and speech improves if we have many phrasal verbs as an arsenal at our disposal!

Learning and Mastering the Use of Collocations

As English as second language (ESL) users, we often think that we do not know enough English words or feel that our vocabulary is limited, which makes us unconfident and eventually disrupts our verbal or written communication. The truth is that we probably have known a lot of English words, and mastering collocations will massively increase our vocabulary.

Here are some ways that we can do to help us learn and master the use of collocations:

- Learn from real-life sources: reading articles, listening to songs, having conversations with your friends. Note down the collocations and write a sentence that is true to you using the phrases.
- Review the collocations regularly by using flashcards or flashcard applications on your smartphone.
- Group the collocations you have learned into similar topics, for example, collocations to describe a study, collocations to describe a person, or collocations to talk about a relationship. After you have about five or ten collocations in a group, write a short paragraph using all the collocations. For example, you can write a short article about the study you are conducting, or the people involved in the study. The important part here is to write something that is true to you.

Practice Makes Perfect

Let's practice! Use at least five of the collocations below in a paragraph to describe your city. You can send us your paragraph if you want. Remember, write something that is true to you.

City skyline	Good value	Residential areas
Cobbled streets	Lined with shops	Volume of traffic
Quaint old buildings	Lively bars	Strewn with litter
Pricey / overpriced restaurants	Relaxed atmosphere	Imposing buildings

*broke out = suddenly started; put off = delay/postpone; see to (sth) = ensure; figure out = to understand or solve (sth)

INA-RESPOND Newsletter

Broken English - A Nightmare for Editor and Author

By: ALY DIANA

COMIC CORNER

Writing our first manuscript in English, especially when we are not an English native speaker can be a nightmare, not only for us but also for editors of journals. Should we stop or run away then? Hmmm, better not. Practice makes perfect, so it's better to keep practicing and avoiding the common errors/mistakes in English. There are some suggestions to produce a better manuscript before submitting it for review.

The 'easiest' way to start is to find similar studies/articles published in good/high impact journals and then try to follow the structure of these articles. The good news is that there is nothing too artistic in writing a manuscript, so we can use the published articles as our template in terms of structure.

Once we have finished, firstly, ask a friend or two who is not related to the study to read our manuscript. If the person can understand what we are trying to tell without asking for further explanations, it means we have done a great job. First hint: ask a reliable friend who knows English well enough and will spend his/her time reading our manuscript.

After we have passed the first hurdle, secondly, let's check our sentences one by one. Let's make sure that every sentence has at least a pair of subject and predicate/verb. There are some other types of common mistakes in making our sentences, such as choppy sentences, run-on sentences, stringy sentences, and dangling participles. So, let's re-check our sentences and fix the mistakes.

Next, let's check the tenses. As the golden rules, in the Introduction, we usually use simple present or present participle tense; and we typically use the past tense in Methods. We often use past participle (mostly used in passive voice) when we present the results (of the 200 approached, 11 were excluded, is shown in table 1); however, we use present verbs when referring to a table/a figure (figure 1 presents). In the Discussion, we usually use the present tense when we talk about other previous studies/papers, but we typically use past tense when we talk about our recent study.

Next, let's check on the usage of article (a/an and the), preposition, singular/plural, and punctuation. As a beginner, it's better to check one thing at one times, so we can really focus on what we want to check and fix. Checking a paper to make sure it's ready to be submitted can be very time consuming, but it will worth it. Well-written paper will increase the possibility of its acceptance by the journal. Once it's accepted, we can feel that all our hard work is meaningful.

Let's start!

Second hint: Most journals offer an editorial service which we can use. However, it's usually quite expensive. If we use the service, please learn from the changes that have been made, so we can use the lesson learn for our next manuscript.

Third hint: Having a collaborator who is a native speaker and good at writing is a big plus. We can learn a lot from him/her. Pay attention on the corrections.

Note:

Choppy sentences: Sentences that are too short and often repeat the same words. They should be combined to make longer/better sentences.

Run-on sentence: A grammatically faulty sentence in which two or more main or independent clauses are joined without a word to connect them or a punctuation mark to separate them.

Stringy sentence: A stringy sentence is made up of several complete thoughts strung together with words like 'and,' 'so,' or 'but.' Stringy sentences are so long that the reader forgets the beginning of the sentence before reaching the end.

“It was a great read, except I collided with run-on sentences, tripped over broken English and got knocked about by a dangling participle.”

INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

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