INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

January 2019

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NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
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INA-RESPOND newsletter

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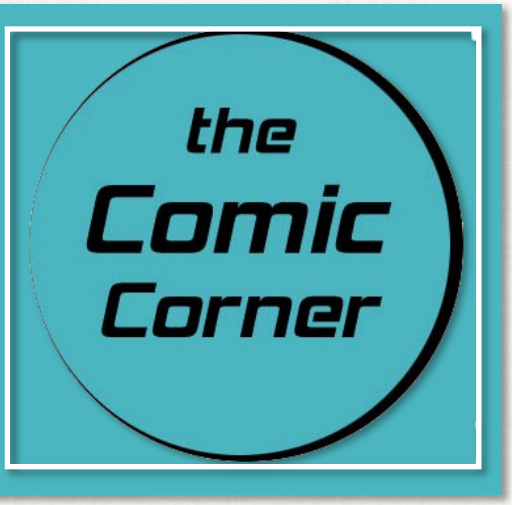
FEATURES



DR. Dr. Irmansyah, SpKJ(K).

H. Clifford Lane, M.D.

dr. M. Karyana, M.Kes.

We would like to wish you the best in 2019 and thank you all for our togetherness to have an outstanding 2018.

When we look at our achievements in 2018, we believe that there is much to be proud of. We have three studies ongoing successfully, the TRIPOD, PEPPES, and Pro-Active, involving more than 20 institutions throughout Indonesia. We have completed the AFIRE study, resulting in several health policy recommendations in the diagnosis and management of infectious diseases. These were presented in "Emerging and Re-emerging Infectious Diseases" seminar at the Ministry of Health last February. Other achievements included disseminating our research findings through international conferences and peer-reviewed international journals, and providing training through three international meetings about 'Ethics in Research,' 'HIV and Co-infections,' 'Data Management using Open Clinica", and in collaboration with Indonesia's PETRI, 'Strategies to Control and Manage Infectious Diseases.' All of these activities in addition to the routine interim analysis and network steering committee meetings have significantly contributed to enhancing research capacities and improving the knowledge of INA-RESPOND's researchers (from our young researchers to experts in infectious diseases), as well as clinicians and researchers from outside the network.

We don't know what 2019 will bring, but we know for sure that we would like to continue towards our goal of making our INA-RESPOND the premier research network in the region by maintaining to conduct high-quality research including two new studies: a community-based schistosomiasis study and a clinical trial on second line anti-retroviral therapy (D2EFT study). We will also continue to enhance research capacities, to provide and disseminate evidence-based health policies, and to participate in global infectious disease research.

We appreciate it and hope that this fruitful collaboration will be beneficial for both countries and may minimize the impact of infectious diseases, which in general will improve human well-being.

"Last but not least, we would like to thank our long-time collaborator, the US-NIAID, led by Dr. Clifford Lane, for co-sponsoring our activities and providing scientific and technical assistance" Dr. Irmansyah.

"NIAID would like to thank the Indonesian Ministry of Health and NIHRD for their collaboration, support, and leadership. We look forward to the successes of our continued partnership." Dr. Lane

EDITOR'S LETTER

First of all, I would like to wish us all a happy new year. May the year 2019 bring us a new spirit, excitement, and success. Our newsletter has gone a long way since it was first published in October 2013. We have published more than 60 issues in the last five years, and what started as a simple and straightforward media of communication has developed into a more exciting and informative way to introduce our network and its activities as well as to disseminate information related to infectious disease and healthy living to its stakeholders, the health communities, and general public. In addition to the 'Sport and Health,' we have some new rubrics in our newsletter, the 'From Our Laboratory' and ''Writing Corner,' to accommodate the growing enthusiasm and interest of our stakeholders. We encourage our network sites' study team members to write and submit the articles to us. Do not hesitate to let us know what topic you are interested in writing. We would be happy to feature your article in our newsletter!

Thank you for your active contributions and support over the years, which keep us motivated and eager. Keep up the good work, and God bless us all.

" The beauty of collaboration in research is in unifying resources to accomplish a job and gain new knowledge more efficiently " - Irmansyah, 2019

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

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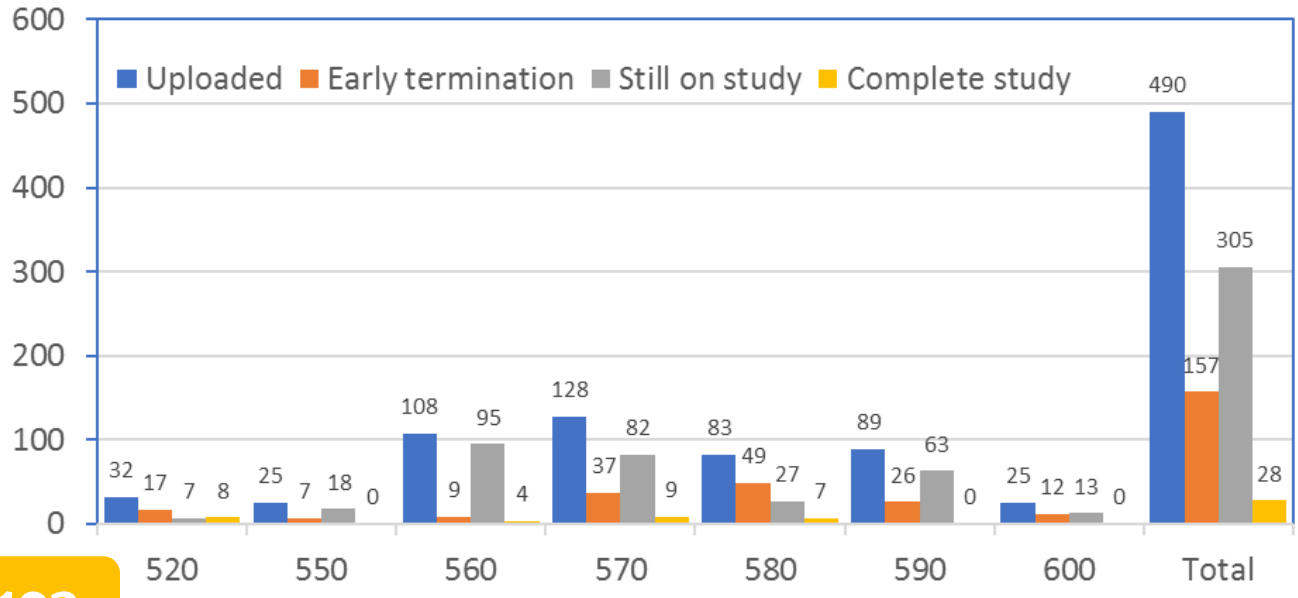

Figure 1. TRIPOD subject data up to 31 December 2018

TOTAL ENROLLED SUBJECTS

Total enrolled subjects for TRIPOD Study are 490 subjects: 32 subjects from site 520, 25 subjects from site 550, 108 subjects from site 560, 128 subjects from site 570, 83 subjects from site 580, 89 subjects from site 590, 25 subjects from site 600. Data can be seen in Figure 1. TRIPOD subject data up to 31 December 2018.

TOTAL ONGOING SUBJECTS

Per 9 January 2019, the total ongoing subjects in TRIPOD study are 305 from the total 490 enrolled subjects. Twenty-eight subjects have completed the study while 157 subjects are terminated early (including death). Therefore, there are still 62.2 % subjects from the total enrolled subjects in the follow-up status.

From the uploaded CRFs, there are seven subjects from site 520 (RS Sanglah Denpasar) who still need to be followed up, 18 subjects from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 95 subjects from site 560 (RSUP dr. Kariadi Semarang), 82 subjects from site 570 (RSUD dr. Soetomo Surabaya), 27 subjects from site 580 (RSUP dr. Sardjito Jogjakarta), 63 subjects from site 590 (RSUP Persahabatan Jakarta), and 13 subjects from site 600 (RSUP dr. Adam Malik Medan).

TRIPOD MANUSCRIPT

TRIPOD study teams are currently preparing the names for authorship of TRIPOD Manuscript. The following are several planned manuscripts: a) focus on the baseline findings; b) treatment outcome and the related affected factors; c) related factors of TB and DM co-morbidity. The team will start working on study data identifications, i.e. previous TB treatment, etc. to prepare for the first manuscript.

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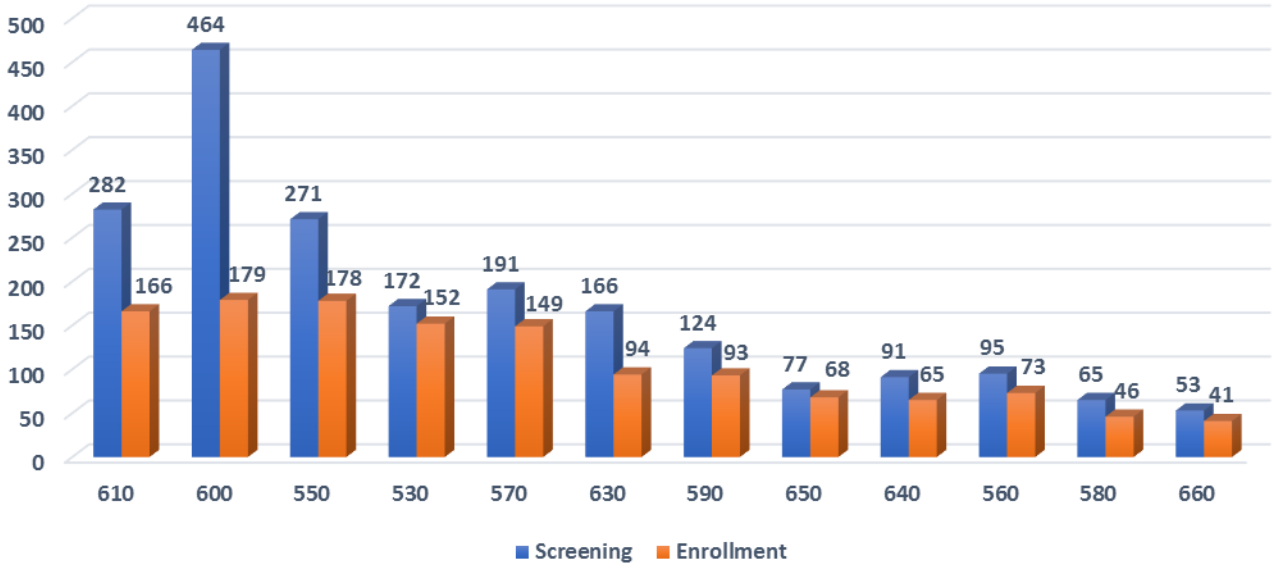
Screening & Enrollment 7 January 2019



By 7 January 2019, all 12 sites as shown in the figure above had enrolled 1,304 subjects consist of 59 pediatrics and 1,245 adults. Sites enrolled 63,57% of screened patients (2,051 screened patients).

Enrollment failure rate was 36,42% from total screening number due to the reasons in the table below:

Currently, there is no Site Monitoring Visit schedule announced for January 2019.

There is some progress in new sites' preparations. Site Preparation Visit (SPV) was conducted at site 510 (Hasan Sadikin Hospital) on 7-9 January 2019 and will be followed up with a Site Initiation Visit on 23-24 January 2019.

Starting off this new year, INA-RESPOND has received some good news. Soedarso Hospital has just signed the agreement of INA104 study as a response of the Site Assessment Visit (SAV) last month. Abepura Hospital in Papua has also given a positive response by sending a research collaboration letter which includes the name of the study team. The Secretariat will conduct SAV to this site soon. We are currently waiting for another response from Maumere Hospital in East Nusa Tenggara province. We hope to be able to include these hospitals in our INA-RESPOND network.

We are also preparing for a SPV to site 670 (Zainoel Abidin Hospital, Aceh) and site 520 (Sanglah Hospital, Bali.)

Reason	610	600	550	570	530	630	590	650	640	560	580	660	Total
1. Suspect HIV	4	-	2	-	-	1	-	-	-	-	-	-	7
2. Refuse to consent	2	-	4	4	3	-	5	-	-	3	-		21
3. Unwilling to comply with the study	2	24	2	3	9	-	-	2	-	12	3		57
4. Plans to move away	1	9	5	-	6	2	3	-	2	3	-	3	34
A. No show	66	248	23	4	15	43	13	-	4	1	2	2	421
B. Busy (in a hurry)	18	4	27	4	8	5	3	6	18	2	11	7	113
C. Has been enrolled	23	-	26	5	-	15	7	1	2	1	-		80
D. Participated in other CT											3		3
E. Hospitalized or unwell	-	-	4	-	-	-	-	-	-	-	-		4
F. Others (e.g. no referral letter from other health facility, equipment trouble)	-	-	-	-	1	6	-	-	-	-	-		7

INA-RESPOND Newsletter

FROM OUR LABORATORY

HIV Serology Examination Methods and Algorithms

By: AGNES R INDRATI

HIV examination is an entrance to access HIV treatment, care, and prevention. It is estimated that half of the people living with HIV do not know their HIV status. HIV examination is often late

The detection of HIV infection is usually done based on the detected HIV antibodies. In the past few years, p24 antigen tests have been carried out for HIV diagnosis.

The most common method used for a screening test is Enzyme-Linked Immunosorbent Assay (ELISA) because the technique is considered as a more suitable method for screening a large number quantity of specimens such as blood donors. The ELISA method develops by using antigens that are labeled as conjugates so that the inspection results are susceptible and can reduce the window period. To further reduce the window period, an examination to detect both HIV antibodies and antigens was created on the 4th generation of ELISA. Using the 3rd generation of ELISA, the window period ranges from 21 days, while using the window period generation of ELISA, the period can be shorter, which is 14 days.

Besides ELISA, another serology method that can be used is the rapid HIV test. This simple method does not need complicated laboratory equipment so that it can be used at the point of care and is an important strategy to expand examination access, to speed up the examination so that the result can be delivered on the same day and to enable a network of referrals and follow-ups. With rapid HIV test, the result can be found in less than 20 minutes. This simple method is very suitable for use in inspection and counseling services and laboratories with limited facilities with not too many specimens per day.

UNAIDS and WHO recommended using the third strategy for HIV diagnosis to maximize accuracy and to reduce the cost needed. While the first strategy is used for the safety of blood use and transplantation, the second strategy is widely used in surveillance.

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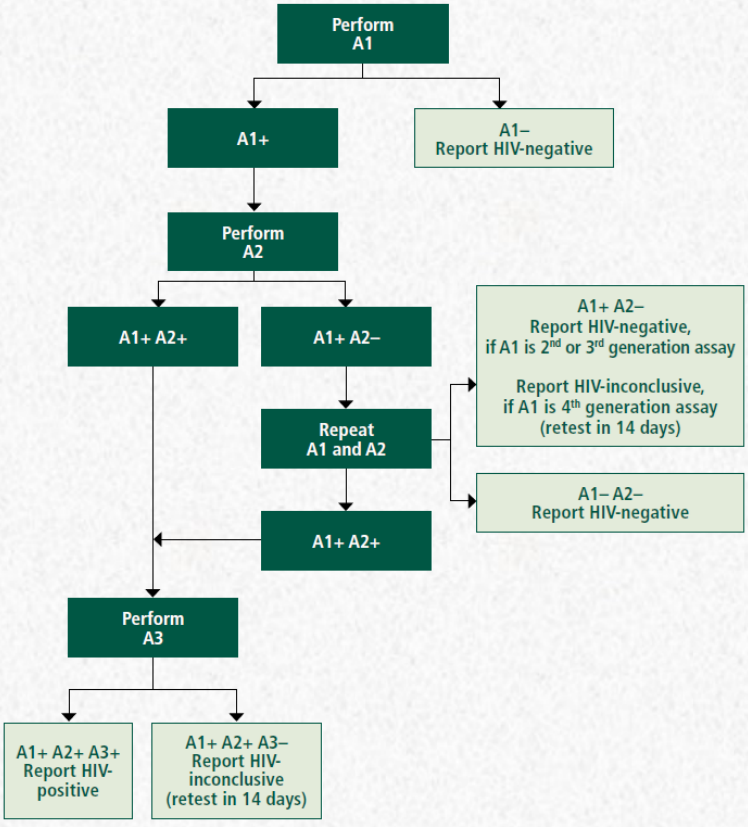
Materials for ELISA can be serum or plasma, while rapid testing can use capillary blood other than serum or plasma. All samples for HIV testing are first examined using ELISA or a rapid test that is the first reagent. Reactive results at the first examination must be re-examined using a second examination. Serums with "non-reactive" results at the first examination are considered "negative" / do not have HIV antibodies. The serum with reactive results at the first examination, but non-reactive at the second examination, must be repeated with both tests.

Serums with "reactive" results on all three examinations are considered "positive" or have HIV antibodies. Serum with different results at the second examination or reactive in the first and second examinations, but non- reactive at the third examination, is considered "indeterminate". Serums that are reactive in the first and non- reactive examinations in the second and third examinations are considered "indeterminate" in individuals who may have been exposed to HIV for at least the last three months and are considered "negative" in individuals who have never been exposed to the risk of HIV infection.

The following figure presents the strategy III HIV screening algorithm.



HIV Diagnosis Algorithm uses strategy III

For Diagnosis of HIV infection diagnosis in asymptomatic individuals with indeterminate results, a second blood sample should be taken at least two weeks after the first examination and examined according to the appropriate strategy. If the second sample continues to give "indeterminate" results, a confirmation check is performed. Confirmation checks can be done using the Western Blot method. The three examinations used in strategy III for diagnosis must be three examinations with different antigen preparations and/or different examination principles. The first examination uses a check with high sensitivity (≥99%) to avoid the occurrence of false negative results, while examinations are used as reagents second and third must have very high specificity (≥98%) to prevent false positives. By serially combining three examinations for HIV diagnosis, the accuracy of the test is high. The number of results that are not suitable or indeterminate should not exceed 5%. If there are more than 5% indeterminate results, the quality of all procedures must be evaluated or the combination of checks must be changed. Serial research algorithms that save costs compared to checking in parallel will also increase the accuracy and reduce the possibility of false positives and negatives.

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INA-RESPOND Newsletter

NS1: The New Player in The Pathogenesis of Dengue Virus Infection

By: M. HELMI AZIZ

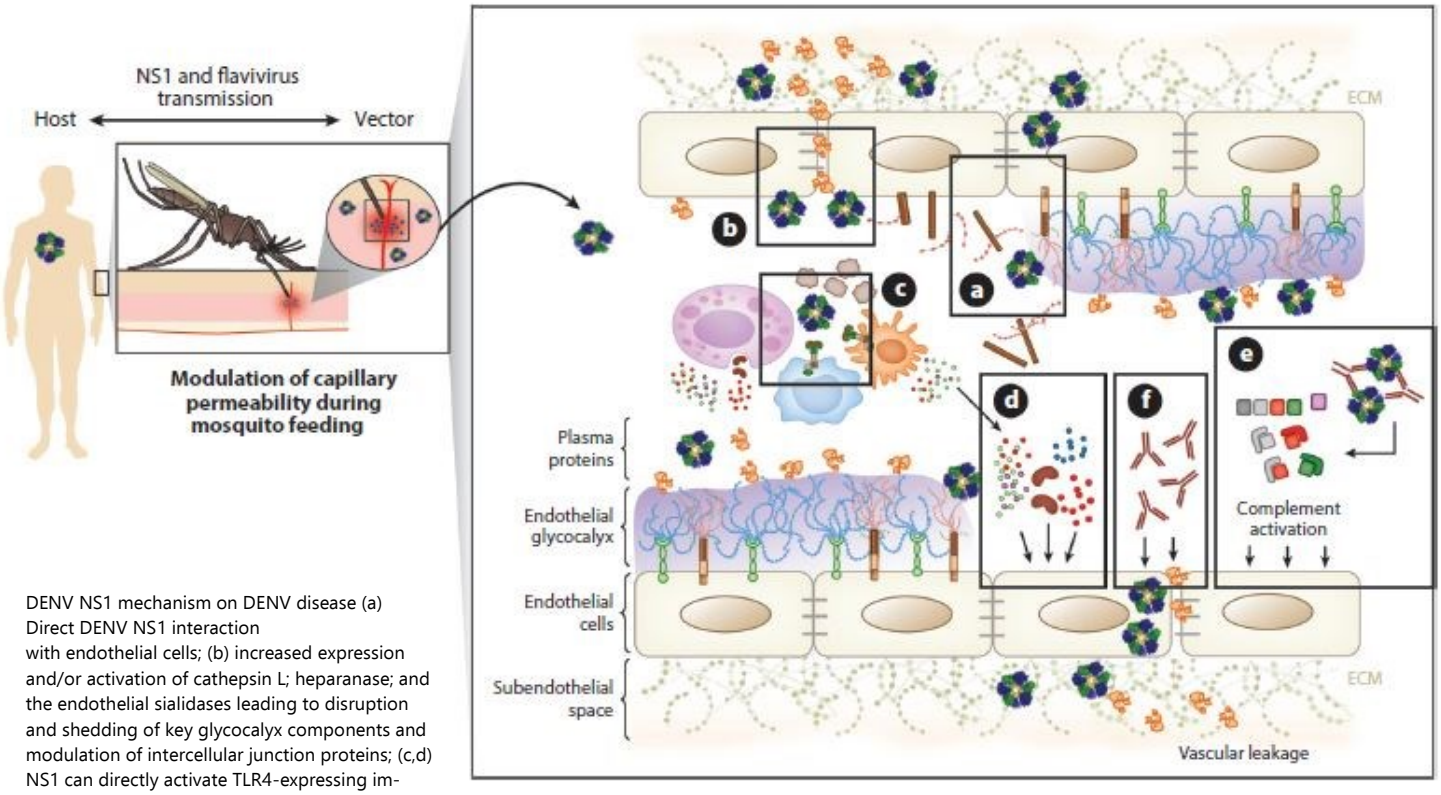
SCIENCE & HEALTH

Dengue is the most ubiquitous mosquito-borne viral disease worldwide with 96 million cases annually, and half of the world's population is at risk of catching Dengue virus (DENV). DENV has four serotypes, and infection with two different serotypes sequentially (secondary infection) can lead to severe dengue infection. The severe dengue infection has been thought due to the antibody-dependent enhancement (ADE) and serotype cross-reactive T cells that contribute to the "cytokine storm." This month's article will review the NS1, the most well-known non-structural protein for diagnosis of DENV infection, regarding its contribution of DENV infection pathogenesis.

DENV is a positive-sense RNA virus which encodes three structural proteins (capsid, premembrane/membrane (prM/M), envelope (E)) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). NS1 gene in all flaviviruses is approximately 1,056 nucleotides and encodes 352 amino acid (aa) protein. Phylogenetic analysis of NS1 aa sequences from flaviviruses (DENV1-4, Zika, West Nile, Japanese Encephalitis, Yellow fever, and St. Louis Encephalitis) revealed variable conservation that ranges from 50–80%.

The differences in the sequences of NS1 makes NS1 useful as a diagnostic tool to distinguish flaviviruses in an endemic area. Not only proven as a diagnostic tool, in recent years' studies it has been shown that the presence of NS1 during DENV infection is associated with severe clinical DENV disease.

DENV NS1 is secreted at a high level during DENV infection as a soluble hexamer which interacts tightly with lipids (triglycerides, cholesteryl esters, and phospholipids). The crystal structure of NS1 seen at high resolution reveals three distinct domains with two domains named the wing domain and β-ladder, the most antigenic regions which serve as the target of humoral immune system recognition. Two researchers from different groups showed that DENV NS1 alone is capable of inducing endothelial hyperpermeability of human pulmonary, dermal, and umbilical vein endothelial cells in vitro. Also, administration of DENV NS1 in a mouse model triggered vascular leak in the lung, liver, and small intestine of mice. These findings suggested that NS1 plays a direct pathogenic role during DENV infection. But how does the Dengue NS1 mechanism work?



DENV NS1 mechanism on DENV disease (a) Direct DENV NS1 interaction with endothelial cells; (b) increased expression and/or activation of cathepsin L; heparanase; and the endothelial sialidases leading to disruption and shedding of key glycocalyx components and modulation of intercellular junction proteins; (c,d) NS1 can directly activate TLR4-expressing immune cells to trigger the secretion of proinflammatory cytokines; (e) NS1 contributes to immune evasion via interaction with components of the complement pathway; (f) Cross-reactive anti-NS1 antibodies binding to platelets and components of the clotting cascade leading to endothelial cell damage via apoptosis.

The first mechanism is the disruption of endothelial hyperpermeability. After secreted by the infected cells, DENV NS1 circulates in the blood and can bind to the surface of microvascular endothelial cells in capillary beds. The interaction of NS1 with endothelial cells results in endothelial hyperpermeability that can be measured by transendothelial electrical resistance in the experiment done in human endothelial cell lines. NS1 increases the expression of sialidases and triggers the activation of cathepsin L, which degrade the endothelial glycocalyx-like layer results in endothelial barrier dysfunction. In addition, studies have evaluated DENV infection patient's sera and found that levels of important endothelial glycocalyx molecules (hyaluronic acid, heparan sulfate, chondroitin sulfate, and syndecan-1) are elevated to a greater degree in the patient with severe disease. Also, the mechanism of endothelial hyperpermeability is provided by NS1 via disruption of the endothelial intercellular junction directly.

The second mechanism is the activation of inflammatory cytokines which plays an essential role in severe dengue pathogenesis. Dysregulation of cytokines production such as TNF-α, IL-10, IL-6, and IFN-γ has been proposed as predictors of disease severity. Administration of DENV2 NS1 in mouse model resulting in significantly higher levels of TNF-α and IL-6 in the blood which may contribute to vascular leak during severe dengue disease. The secretion of the inflammatory cytokines is due to activation of murine bone marrow-derived macrophages and human peripheral blood mononuclear cells via Toll-like receptor 4 (TLR4).

Other interesting roles of NS1 role in DENV pathogenesis are related to immune complement system, NS1 cross-reactivity, and NS1-induced apoptosis. NS1 protects the DENV from lysis through complement-mediated neutralization by binds to the C4 and recruits and activates the protease C1s. Hence, NS1 promotes more viral replication and potentially contributes to endothelial injury. Cross-reactivity of pathogenic anti-NS1 antibodies also contributed to DENV pathogenesis. Murine anti-NS1 antibodies bind to human platelets, thrombin, plasminogen, and endothelial cells in vitro. Besides, anti-NS1 antibodies also trigger endothelial cells apoptosis through nitric oxide production.

Several studies have demonstrated the multifactorial role of NS1 in DENV disease. Hence, more attempts are needed to elucidate more the full mechanism of action of NS1. By understanding the mechanism of NS1 pathogenesis, soon, NS1 could serve as a target for therapeutics and vaccine design candidate for DENV disease.

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INA-RESPOND Newsletter

Physical Activity And Exercise Guideline In Breast Cancer Patients

By: Dr. Septia Mandala Putra

Dr. Septia Mandala Putra
(Sport Physician)

Introduction

Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall. There were over two million new cases in 2018.1 And also causes the highest number of cancer-related deaths among women. In 2018, it is estimated that 627,000 women died from breast cancer – approximately 15 % of all cancer deaths among women.[2] Primary prevention of breast cancer is an area of considerable interest on many levels including scientific, economic, and political. Lifestyle and environmental variables are pivotal influences in the development of breast cancer. Some risk factors associated with developing breast cancer are obesity and physical inactivity. Educating the public about these risk factors and providing interventions to modify the exposure to these risk factors may offer a viable route to decrease the burden of breast cancer.

Obesity as the risk factor

Nearly all of the evidence linking obesity to cancer risks comes from large cohort studies. Many studies have shown that in postmenopausal women, a higher body mass index (BMI) is associated with a modest increase in the risk of breast cancer. For example, five-unit increase in BMI is associated with 12% increased risk of breast cancer.[3] In *RISK-ESDAS (Riset Kesehatan Dasar)* 2018 in Indonesia, obesity in Indonesia increased from 14.8 % to 21.8% from 2013 to 2018. [4] The mechanisms through which obesity influences the development and progression of breast cancer are not fully elucidated. However, several factors such as increased estrogen, a concentration of various members of the insulin family, and inflammation associated with adiposity are the essential factors in this relationship. Emerging research has also begun to focus on the role of adipokines (adipocyte-secreted factors) in breast cancer. Leptin secretion is directly related to adiposity and is believed to promote breast cancer directly and independently. As leptin is secreted from white adipose tissue, any intervention that reduces adiposity may be favorable. [5]

Role of physical activity and exercise in breast cancer

Many of the lifestyle choices thought to help prevent breast cancer are either directly or indirectly related to energy balance. Energy balance is most often described as calories consumed versus those expended during physical activity or exercise. For this reason, caloric intake and physical activities/exercises are among the energy balance lifestyle choices which may have an enormous potential to reduce breast cancer. [6]

Exercise has been shown to be a safe and effective adjuvant therapy for breast cancer. Providing that energy expenditure is in line with or exceeds energy intake, training can positively influence adiposity and overall body composition. Reduced adiposity has been shown to reduce circulating leptin concentration.

Some studies have shown that women who are physically active before and after diagnosis of breast cancer have better cancer-related and overall survivals compared to women who lead a more sedentary lifestyle. Aerobic exercise has been identified as the most significant predictor of maintenance of pre-chemotherapy weight. Additional benefits of aerobic exercise include increased functional capacity, reduced fatigue, fewer sleep disturbances, decreased nausea, and improvement in mood. [7]

The evidence for an association between physical activity and breast cancer has been classified as convincing. The

results from case-control studies and cohort studies have shown that invasive breast cancer risk is reduced by 20–40% among physically active women. One of the earliest studies, a case-control study of women aged 40 years or younger, showed a dramatic reduction risk (approximately 50%) among women who had about four hours activity per week during their reproductive years.

Exercise also has a positive effect on breast cancer evolution, including prevention, medical treatment, and aftercare clinical settings. Plus, elevated serum levels of CEA and CE15 -3 as prognostic were identified in patients with breast cancer. Esfahbodi et al. found that eight weeks intervention of aerobic exercise can improve body composition without increasing the level of fatigue or stress values and could reduce CA15-3 insignificantly. [8]

Exercise for breast cancer: a common guideline [9]

A Pre-Exercise assessment to evaluate for any effects of disease, treatments, and comorbidities is recommended for all people before starting an exercise intervention. This assessment can allow the clinicians and the people with cancer to feel safer and more secure before an exercise regimen commences. They can also ensure that the individual is aware of possible vulnerabilities associated with their condition.

Canadian Society for Exercise Physiology and the American College of Sports Medicine have already issued some recommendations:

- A goal of 150 minutes of moderate-intensity aerobic exercise spread over three-five days and resistance training at least two days per week.
- Resistance session should involve major muscle groups two-three days per week (8–10 muscle groups, 8–10 repetitions, two sets).
- Each session should include a warm up and cool down exercises.

People living with cancer can safely engage in a moderate amount of exercise while on active treatment or after completion of therapy.

Moderate amount of muscular and aerobic fitness/exercises are recommended to improve quality of life (QOL).

It is recommended that, where possible, people living with cancer exercise in a group or supervised setting, because that environment might provide a superior benefit.

Conclusion

Overall, physical activity and exercise have excellent response in preventing and treatment of breast cancer. Before you do any physical activity and exercise, you should consult it to your doctor, especially the oncologist and sports medicine doctor. To know your capability of doing a task, undertaking a pre-exercise fitness assessment is a must.

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INA-RESPOND Newsletter

Misspelling: Seems Trivial, But Can Be Fatal

By: AMELIA GHANI

WRITING CORNER

One of the most common problems in manuscript writing is misspelling. Misspelling can be caused by the authors' not knowing the right spelling to some words or can be a typo that they do not pay attention to. Misspelling does not only happen among Indonesian writers, but it also applies to writers from English-speaking countries.

The invention of standalone spell checkers in 1980s, followed by the embedded version in the word processing software such as in Word95 in 1995 made the life of the writers a lot easier, and misspelling words should become extinct. However, though spell checkers are helpful, the complexity of the medical terminology ensures that at least some words are still misspelled. Also, spell checkers are not designed to detect the slight differences of what the author would like to say and homonyms such as your/you're, its/it's, their/they're/there, and wood/would.

Usually, a manuscript is written by multiple authors so they should find misspelled

Source: Nielsen Norman Group. All rights reserved.

words that are missed by the spell checkers. Before the submission, authors may also ask their friends to proofread their manuscripts once or twice. The next screening is done by the reviewers and the editor of the journal, and when it is accepted, the last selection is made by an editorial staff. Referring to this long process, the chance for misspelled words is small but still might occur.

Several examples related to misspelled words are:

- Those that can easily be found by a spell checker: faculity/ faculaty (faculty); patiens (patients); bloting (blotting); infacted (infected); Mann-Whitnet Test (Mann-Whitney Test); indentified (identified); precesion (precision); colculation (calculation); and standart (standard).
- Those that should be found by the co-authors in medical dictionary or lab manual book: Twen-20 (Tween-20); abominable pain (abdominal pain); axe (ask); illicit (elicit); plural (pleural); lime disease (Lyme disease); inhalator (inhaler); acid reflex (acid reflux); callous (callus); sinuses (sinusitis); myocardial infraction (myocardial infarction).
- Those that a spell checker might miss: socialite/socialist, definitely/defiantly, marital/martial, tortuous/torturous, septic/sceptic/skeptic, causal/casual, dessert/desert, and heroin/heroine
- Those that may be missed even by the reviewers and editorial staff: pruritis (pruritus), lactrodectus (Latrodectus). The misspelled 'pruritis' was found in 149 articles, including those written by scientists from Harvard and Johns Hopkins, 7% of them published in dermatology journals, 60% from English speaking countries, and four articles published in Cochrane reviews that require an extensive scholarship to produce. Latrodectus, a widow spider, was repeatedly misspelled as lactrodectus in many articles, even written by experts. It may be influenced by the familiarity of words involving with prefix 'lacto' for milk and dairy product. Hence, this genus might be misunderstood as 'milk widow spider.'

Misspelling seems like a trivial problem in writing, but its impact can be fatal, especially if the authors do misspell the authors' names. When a scientific article containing the misspelled names has been published, usually it cannot be taken down anymore, and the authors will not be able to change the misspelled names. For example, the misspelled surname 'Wicaksana' instead of 'Wisaksana' in the article titled 'Evidence of human hantavirus infection and zoonotic investigation of hantavirus prevalence in rodents in western Java, Indonesia,' or Paterson instead of Petersen in 'Decline in Weight and Incident Mild Cognitive Impairment.' However, not all journals have the policy to publish an erratum to correct this mistake. The misspelling of names also occurs in manuscript writing. For examples, the name of the father of American surgical education, Halsted, is often misspelled as Halstead; and Peters anomaly, a disorder of the eye, is often misspelled as Peter anomaly.

Source: Pinterest

Misspelling is unprofessional, aesthetically unpleasing, can leave a negative impression to the reviewers who may return the manuscripts to the authors for revisions, and will prevent the citation from being retrieved. Therefore, please use your spell checker and a medical dictionary, ask other authors to carefully read the manuscript, and ask your peer to proofread before submitting it.

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Newsletter

Post Hoc Procedure: Bonferroni Correction

By: ALY DIANA

Sometimes we have too much fun when we do some statistic tests and forget that there are some rules that we should consider. This time, let's remind ourselves about the post hoc procedure and how to apply it to our analysis if needed.

In a simple condition with two groups of samples (or two variables) and the null hypothesis of no difference between the two groups, we can perform a statistical test to see whether the means between the two groups are different (rejecting the null hypothesis) or not. We set the level of significance (α) at 0.05 which means that there is a 5% chance of getting your observed result if the null hypothesis were correct. It does not say that there is a 5% chance that the null hypothesis is correct.

When we have three variables and want to compare each pair (var1 vs. var2, var1 vs. var3, var2 vs. var3), we will have to perform the statistical test 3 times. Therefore, the probability of getting type I error from these multiple comparisons is 0.95 x 0.95 x 0.95 = 0.857. In other words, the overall error rate (α) increased from the acceptable limit of 0.05 to 14.3. The family-wise error rate from a series/family of statistical test can suggest that each addition of test performed increased the probability of getting a significant result even with an addition of merely one or two variables. This is due to the result of the number of combinations generated according to the combination equation. Say that we have five variables now, the number of statistical tests to perform rises to 10. The family-wise error rate = 1 – (0.95)10 = 0.40. This is why we need an adjustment/correction to the level of significance (α).

Post hoc tests consist of pairwise comparisons that are designed to compare all different combinations of the treatment groups with the control of the familywise error by correcting the level of significance for each test to make sure that the overall Type I error rate (α) across all comparisons remains at 0.05. There are many types of post hoc analyses ranging from a single-step to multiple-steps and from small to a large number of comparisons (e.g., Bonferroni procedure; Holm-Bonferroni procedure; Shaffer's modified Bonferroni; Dunnett's test; Tukey's Honest Significant Difference test; Duncan's multiple range tests; Fisher's least significant difference; etc.) The classic and most straightforward approach is the Bonferroni procedure/correction.

Instead of using 0.05 for our familywise α, we use a lower value. Bonferroni correction adjusts the α for each test by dividing the desired familywise α by the number of statistical analyses (corrected α = familywise α/n). This correction results in a smaller p-value for the significance cut off thus lowers the area where the null hypothesis can be rejected. For example, we have 25 combinations. After the Bonferroni correction, the α level for each comparison is 0.05/25 = 0.002. Consequently, a significant result is only obtained when the p-value is below 0.002 or null hypothesis will be rejected if the p-value <0.002.

Bonferroni correction is widely acceptable but limited for a small number of multiple comparisons – less than ten comparisons; as the power reduced in a larger set of tests. Another disadvantage of the Bonferroni procedure is its conservative nature – the relative difficulty in rejecting the null hypothesis. Therefore, if we deal with a large number of comparisons, we can check other procedures listed above.

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COMIC CORNER

I wish 2019 gives you wonderful moments to cherish and to store in your heart to create wonderful memories that you would like to look back upon every now and then.

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