INA RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

Newsletter October 2016

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In This Issue

Rapid Urine Lipoarabinomannan Test

Tuberculosis is the leading cause of HIV/AIDS-related deaths globally. The international community has committed to ending the HIV/AIDS and TB epidemics by 2030. New diagnostic tools are urgently needed to avert deaths from undiagnosed HIV-associated TB. Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have been developed as potential point-of-care tests (POC) for TB.

Although simple assays that detect lipoarabinomannan (LAM) in urine have been commercially available for years, their specific role and utility were initially misunderstood. In this article, we would like to dig deeper into the rapid urine lipoarabinomannan test as urine LAM detection

emerged as a means for rapid diagnosis of TB in people living with HIV and advanced immunodeficiency.

Page 4

Data Mining: Looking for a Hidden Treasure in a Forgotten Past

The term "data mining"has been around for some time. However, there are still many people, especially researchers who do not know about it. Let's find out together what data mining is in this month's comic corner article

Page 7

Save The Date

Important Events & Meetings

4 – 8 October	ATS MECOR Course 2016 Hotel Harris, Bekasi
18 – 21 October	International Health Symposium, NIHRD

October Birthday

2 Oct	Dr. Debby Intan Permatasari	RA INA101 Site 540
5 Oct	Ms. Linda Oktabriana	LT INA102 Site 580
11 Oct	Ms. Ni Nyoman Eriyanti	LT INA101 Site 520
15 oct	dr. Ninny Meutia Pelupessy	Site PI INA101 Site 550
16 Oct	dr. Dwiyanti Puspitasari	Co-PI INA101 Site 570
	Ms. Salfia Dian Lastari	Secretariat
17 Oct	Ms. Deni Peppy R. Butarbutar	Secretariat
20 Oct	dr. Abu Tholib Aman	NSC at Site 580
21 Oct	dr. Nurhayana Sennang	Co-Pi INA101 Site 550
	Mr. Handoko Setiawan	LT INA101 Site 540
26 Oct	dr. Syndi Siahaan	RA INA101 Site 510
28 Oct	Mr. Tri Kusuma Wardhani	LT INA102 Site 560
30 Oct	dr. Iman Firmansyah	Co-PI INA101 Site 540

Announcement

The Ministry of Health, Republic of Indonesia held the 3rd International Symposium of Health Research and Development on Oct 18- 21 at Misistry of Health & NIHRD, Jakarta

The theme of the symposium is "*Masyarakat Hidup Sehat, Indonesia Kuat" (*Healthy Society, Strong Country [Indonesia]). The INA-RESPOND was invited to give presentations. We were all excited as we had the opportunity to share our study results in this event!

INA-RESPOND Study Updates

By dr. Anandika Pawitri,
dr. Nurhayati

AFIRE Study (INA101) Updates

	Site 520 Denpasar	Site 560 Semarang	Site 580 Yogyakarta	Site 510 Bandung	Site 550 Makassar	Site 570 Surabaya
Activation status	Jul 15	Aug 12	Aug 14	Sept 04	Oct 04	Dec 27
Actual FPFV* date	Jul 18	Aug 19	Aug 26	Sept 04	Oct 16	Jan 3, 2014

Site 510 – RSUP dr Hasan Sadikin, Bandung
Site 520 – RSUP Sanglah, Denpasar
Site 530 – RSUPN dr Cipto Mangunkusumo, Jakarta
Site 540 – RSPI Prof Dr Sulianti Saroso, Jakarta
Site 550 – RSUP dr Wahidin Sudirohusodo, Makassar
Site 560 – RSUP dr Kariadi, Semarang
Site 570 – RSUD dr Soetomo, Surabaya
Site 580 – RSUP dr Sardjito, Yogyakarta

Finally, all subjects have completed their follow-up visits! A lot of experiences and lessons are learnt from this first INA-RESPOND study, and at this moment, we would like to thank all site team members for the cooperation, dedication, and commitment given. Currently, all site team at sites are busy completing the CRFS, answering queries, sending specimens, and doing many other things for this study while all the specimens are being tested at reference lab to identify etiologies.

Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.net/EdmFile/getfile/797233
For further information about this study please go to: http://www.ina-respond.net/afire-study/

Sepsis Study (SEA050) Updates

It has been a real pleasure to work with all the site research team in Indonesia as well as those in Thailand and Viet Nam. The research team contributions to the study have led to a good result. The end of screening and enrollment in Sepsis study is not the end of our research journey. Manuscripts are being developed by the research team to find more effective ways of managing the disease and explore more research possibilities.

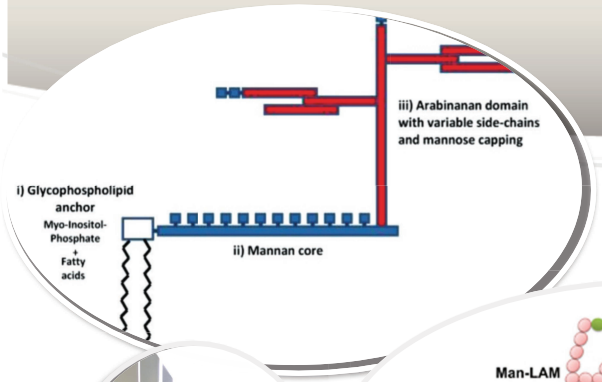
This article will be the last of the Sepsis study updates.

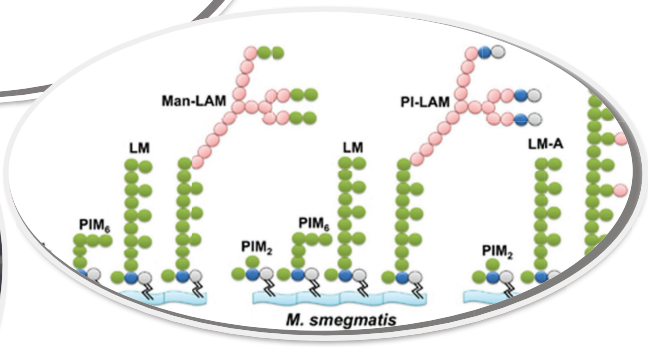
See you in the next study!

Research means that you don't know, but are willing to find out

Charles Kettering

Rapid Urine Lipoarabinomannan Test





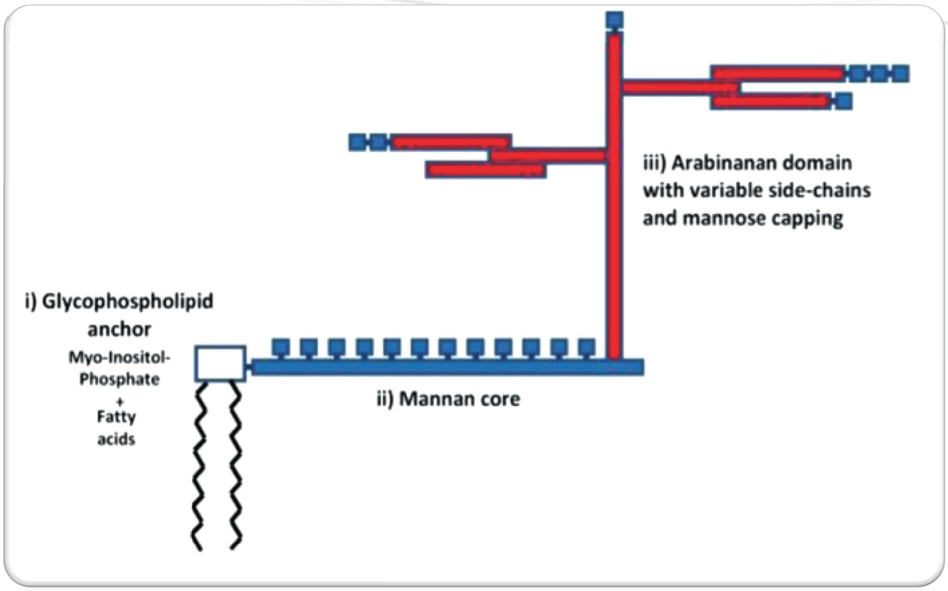
By:

dr. I KetutJaya Ningrat

Key global priorities for tuberculosis (TB) care and control include improving case-detection and detecting cases earlier, including cases of smear-negative disease which are often associated with co-infection with the human immunodeficiency virus (HIV) and with young age. In 2014, an estimated 1.2 million (13%) of the 9.6 million people who developed TB worldwide were HIV-positive. The African Region accounted for 73% of the estimated number of HIV-positive incident TB cases. Globally, people living with HIV are 26 times more likely to develop TB disease than those who are HIV-negative. Beginning in the 1980s, the HIV epidemic led to a major upsurge in TB cases and TB mortality in many countries, especially in southern and eastern Africa. TB occurs early in the course of HIV infection and shortens patient survival if not rapidly diagnosed and treated. Many people infected with HIV in developing countries develop TB as the first manifestation of AIDS.

Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have been developed as potential point-of-care tests (POC) for TB. A number of mycobacterial antigens can be detected in the urine of patients with pulmonary TB, but the most promising of these to emerge is the cell wall lipopolysaccharide lipoarabinomannan. (LAM) Urine-based testing has advantages over sputum-based testing because urine is easy to collect and store, and lacks the infection control risks associated with sputum collection. LAM is an attractive diagnostic target as urine processing requires limited infection control measures, presence of LAM in urine is indirectly related to human immune response, and its detection process is amenable to inexpensive POC platforms. Owing to suboptimal sensitivity, current urinary LAM assays are deemed unsuitable as general screening tests for TB. However, unlike traditional TB diagnostic methods, they demonstrate improved sensitivity in HIV-TB co-infection which further increases with lower CD4 counts.

A LAM antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells. LAM appears to be present predominately in people with active TB disease and has shown only low cross-reactivity with nontuberculous mycobacterial infections. The major Mtb surface antigen is lipoarabinomannan (LAM), which is the major glycolipid surface component of the Mtb cell wall and may account for up to 15% of the total bacterial weight. LAM consists of a mannan polysaccharide backbone with branched oligoarabinosyl containing saccharide side chains; the former is covalently linked to a phosphatidyl inositol lipid moiety



(figure 1). During TB disease LAM in a soluble form is released both from metabolically active and degrading bacterial cells. Hence, we assumed that in active TB disease LAM occurs in serum and subsequently may be cleared through the kidneys and occur in urine in an antigenically intact form. Furthermore, as LAM is a carbohydrate antigen, and thus inherently heat-stable, LAM may be detectable by sensitive immunological techniques, even after heat treatment of urine samples. At least in theory, the amount of LAM in the urine should reflect the bacterial load, metabolic activity and/or rate of degradation of the bacteria, and hence permit a semi-quantitative assessment of the infectious status and response to antibacillary treatment.

The internal segments of arabinans, as they appeaR, consist of linear 5-linked a-D-Araf residues and some branched 3,5-linked a-D-Araf units substituted with 5-linked a-D-Araf residues at both branched positions (figure 2). The nonreducing terminal regions of the arabinans also contain 3,5-linked a-D-Araf residues substituted at both branched positions with the disaccharide β-D-Araf- (1→2)-a-D-Araf. In the present study, several lines of evidence indicate that structural features within the terminal branched hexa-Araf arrangement constitute the epitope of mAb CS-35 and possibly many like antibodies.

Lipoarabinomannan and related glycoconjugates found on the cell wall of *Mycobacterium tuberculosis*, *Mycobacterium smegmatis* and *Corynebacterium glutamicum*. Biochemical analysis of the mycobacterial cell wall suggests that different acylated variants of di- and hexa-mannosylated PIMs, Ac_1/Ac_2PIM_2 and PIM_6, and the higher glycosylated polymers lipomannan and lipoarabinomannan accumulate in the cell wall. In these glycoconjugates, phosphatidyl-*myo*-inositol (phosphate in gray and inositol in blue) acts as an anchor to the plasma membrane and further glycosylated by Man*p* (green) and Ara*f* (pink) sugars yielding different forms of PIMs, lipomannan and lipoarabinomannan that are species specific (figure 2). In *M. tuberculosis* and other pathogenic mycobacteria, lipoarabinomannan is capped by mono, -di or -tri a(1→2)-Man*p* units, resulting in Man-LAM, while in nonpathogenic *M. smegmatis*, lipoarabinomannan is terminated by phospho inositol, yielding PI-LAM.

Published studies have reported much higher mortality rates among HIV positive individuals with low CD4 counts who have detectable urinary LAM using the commercially available lateral flow urine LAM assay (LF-LAM) compared with LF-LAM negative individuals. The LF-LAM assay if accurate, could therefore be a useful tool to facilitate the early initiation of anti-

(continued)

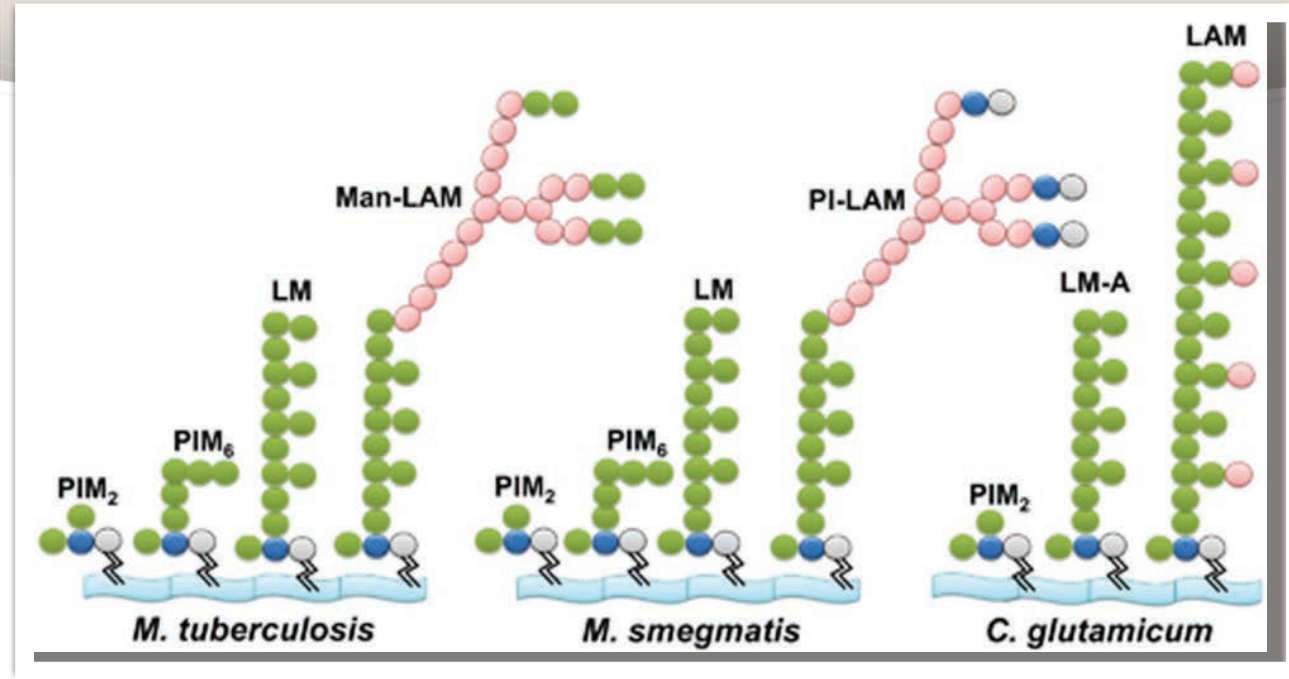


Figure 2: Lipoarabinomannan Structure

TB treatment and help reduce mortality in this patient group. HIV-positive patients with TB disease may be missed for the following reasons: sputum bacillary load is typically low in these patients; they may not be able to provide sufficient and high quality sputum specimens; and a substantial proportion of these patients have extrapulmonary TB without pulmonary TB. Due to high rates of mortality among this patient group, if accurate, a urinary LAM assay would be a useful tool to facilitate the early initiation of anti-TB treatment and thus people with HIV-TB co-infection who are difficult to diagnose with TB using traditional diagnostic methods may benefit.

In response to requests from end-users for guidance on the appropriate use of the LF-LAM assay, its increasing use in high-burden countries and given the potential of the assay to help reduce mortality in HIV positive individuals, WHO commissioned a systematic review of the use of the LF-LAM assay for the diagnosis and screening of active TB in people living with HIV. Given the test is easy to perform, requires minimal biosafety requirements, is inexpensive and in response to its increasing use in HIV prevalent settings, it was considered necessary to develop clear guidance for which patient populations are suitable to test, to avoid having test applied inappropriately.

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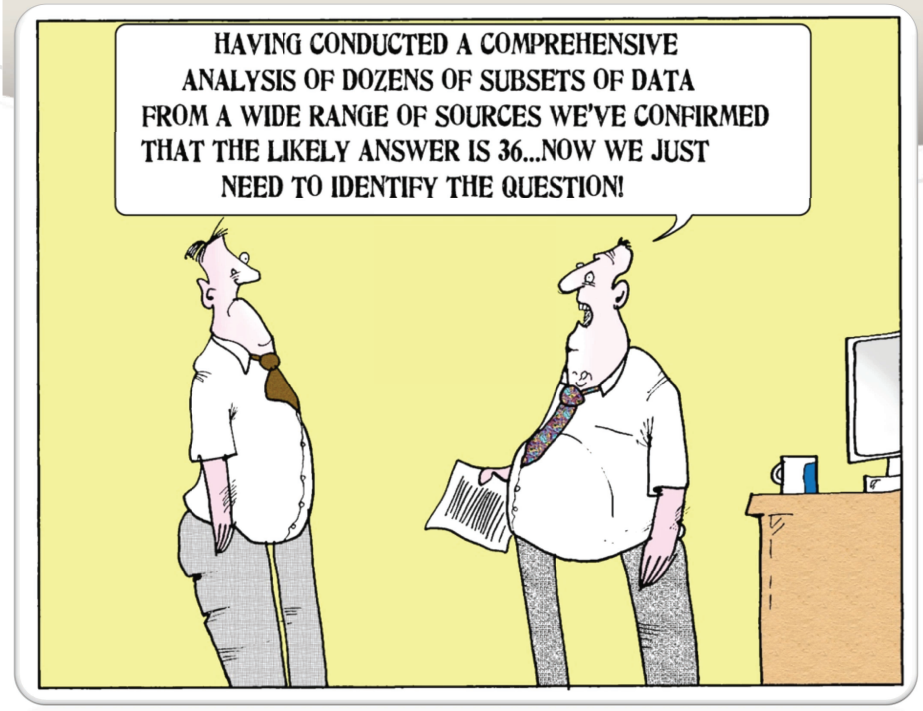

Data Mining: Looking for a Hidden Treasure in a Forgotten Past

By

dr. Aly Diana

In the last month, I have heard about data mining several times from random sources. Out of curiosity, I searched for the term and found many references on this topic; and surprisingly it has been out there for more than 2 decades. So, in this article I will try to summarize the basic concept of data mining (also known as Knowledge Discovery and Data Mining (KDD)) especially in the field of medicine and healthcare; the potentials of this approach for our advantages; and things to avoid while doing data mining.

Data mining is the application of specific algorithms for extracting patterns from data. In contrast with the conventional/classical approach of hypothesis testing; KDD works from a different perspective. While in hypothesis testing we usually formulate a research hypothesis, collect relevant data, and then do a statistical test; in data mining we search for relationships and global pattern that existed in the large databases, but still hidden. Using various methodologies (such as: statistics, database management, pattern recognition, machine learning, data visualization, optimization, and high-performance computing), KDD extracting important/significance information from rapid growing databases.

Healthcare data (e.g.: medical records) are a perfect example of growing databases which mostly sitting there doing nothing. However, these data are actually very useful to improve services if we can utilize the data using an appropriate KDD technique. By the end of the extraction, the data should deliver more accurate and personalized clinical 'answer' to improve the quality and efficiency of care. One example of the most initial studies using KDD is data mining project at Duke University Medical Centre with objective to identify factors that will improve the quality and cost effectiveness of perinatal care. In this case, it is clear that an exploration of the hidden treasure will give direct benefits for both health providers and users of healthcare.

Increasing popularity of KDD lay on the opportunities of using available data to answer some burning questions. In some sense it means that we can reduce costs and times by not doing the data collection process all over again from the scratch. The KDD process itself, containing data preparation, data selection, data cleaning, incorporation of appropriate knowledge, and proper interpretation of the results of mining, are essential to ensure that useful knowledge is derived from the data. Although the KDD process is involving numerous steps, it is still considered as an effective way to verify or discover a new theory/knowledge.

Nevertheless, KDD approach can go the wrong way when the steps are not properly followed. Blind application of data-mining methods (commonly mentioned as data dredging/data fishing/data snooping/p-hacking in the statistical literature) can be a dangerous activity, easily leading to the discovery of meaningless and invalid patterns. Automatically testing huge number of hypotheses by exhaustively searching for combinations of variables that might show a correlation without having plausible biological explanations is one example of blind application which should be avoided.

Closing remarks: KDD might be the most sensible approach to utilize the huge amounts of clinical data that have been collected since a long time ago. However, we need to be very meticulous in performing the KDD process. Please remember KDD is only a useful tool, but the way we (as researchers) use the tool will determine how useful or useless the results are.

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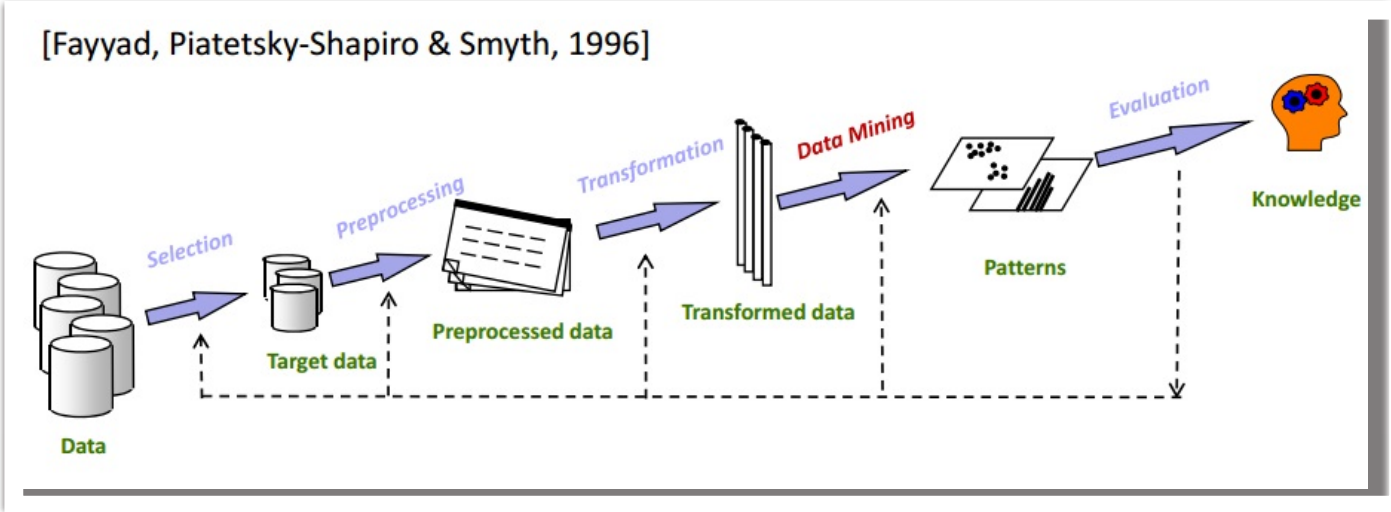

An Overview of The Steps That Compose the KDD Process